Vol. 14 AUGUST, 1943 No. 2

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

EDITORS

ALTON OCHSNER, New Orleans OWEN W. WANGENSTEEN, Minneapolis

ASSOCIATE EDITOR

ALFRED BLALOCK, Baltimore

CONTENTS

Original Communications

A Consideration of the Nonoperative Treatment of Cardiac Tamponade Resulting from Wounds of the Heart. Alfred Blalock, M.D., and Mark M. Ravitch, M.D., Baltimore, Md. ---- 157

Nonpenetrating Abdominal Trauma. Emerson Crosby Kelly, M.D., Albany, N. Y. ---- 163

The Therapy of Shock in Experimental Animals With Serum Protein Solutions, II. Fate in the Body of Concentrated and Dilute Serum and Saline Solutions. E. E. Muirhead, M.D., C. T. Ashworth, M.D., L. A. Kregel, M.D., and J. M. Hill, M.D., Dallas, Texas ---- 171

Clinical Experience With Thrombin as an Hemostatic Agent. R. T. Tidrick, M.D., W. H. Seegers, Ph.D., and E. D. Warner, M.D., Iowa City, Iowa ---- 191

Metabolic Studies in Patients With Cancer of the Gastrointestinal Tract. VI. Disorders in Alimentary Digestion and Absorption in Patients Who Have Undergone Total Gastrectomy for Carcinoma of the Stomach. P. E. Rekers, M.D., George T. Pack, M.D., and C. P. Rhoads, M.D., New York, N. Y. ---- 197

Unilateral Decapsulation of Kidney for Transfusion Oliguria. Spencer C. Flo, M.D., and Harwood W. Cummings, M.D., Greenfield, Mass. ---- 216

Urinary Retention Following the Combined Abdominoperineal Resection. Frederick A. Coller, M.D., and Peter F. Eastman, M.D., Ann Arbor, Mich. ---- 223

Tissue Reactions to Medicaments Used in the Local Treatment of Burns. Mark E. Maun, M.D., Richard C. Schneider, M.D., Matthew A. Pilling, M.D., and John Winslow Hirshfeld, M.D., Detroit, Mich. ---- 229

The Relationship of Acute Anemia to Wound Healing. E. L. Besser, M.D., and J. L. Ehrenhaft, M.D., Iowa City, Iowa ---- 239

Malignant Neoplasms of the Spleen. Paul F. Hausmann, M.D., and Fred W. Gaarde, M.D., Rochester, Minn. ---- 246

The Use of Curare in the Treatment of Tetanus. Stuart C. Cullen, M.D., and C. S. Quinn, M.D., Iowa City, Iowa ---- 256

The Use of Curare for the Improvemet of Abdominal Muscle Relaxation During Inhalation Anesthesia. Stuart C. Cullen, M.D., Iowa City, Iowa ---- 261

Preliminary Observations Concerning Paravertebral Injection of the Sympathetic System in Hypertension. Henry G. Schwartz, M.D., and Thomas Findley, M.D., St. Louis, Mo. 267

Traumatic Rupture of the Duodenum. Jacob Sarnoff, M.D., and Benjamin H. Oremland, M.D., Brooklyn, N. Y. ---- 272

Traumatic Chylothorax—A Case Treated With Intravenous Chyle. Edward Schnug, M.D., and Joseph Ransohoff, M.D., Cincinnati, Ohio ---- 278

Carcinoma of the Parathyroid Gland. Karl A. Meyer, M.D., F.A.C.S., and Alex B. Ragins, M.D., Chicago, Ill. ---- 282

Arteriovenous Fistula of the Common Femoral Vessels With Extreme Dilatation of the External Iliac Vein. James R. Watson, M.D., and R. B. Miller, M.D., Pittsburgh, Pa. 296

Leg Ulcers as a Complication of Caisson Disease. S. Thomas Glasser, M.D., F.A.C.S., New York, N. Y. ---- 302

A New Simple and Rapid Method for Hernial Sac Ligation. Robert Lich, Jr., M.D., M.S., and Ralph B. Samson, M.D., Pittsburgh, Pa. ---- 306

Recent Advances in Surgery

Sulfonamides in Surgery. Victor Richards, M.D., San Francisco, Calif. ---- 308

Book Reviews

Book Reviews ---- 320

Published by THE C. V. MOSBY COMPANY, St. Louis, U. S. A.

Copyright 1943 by The C. V. Mosby Company

SURGERY

ADVISORY COUNCIL

DONALD C. BALFOUR, Rochester, Minn.
VILRAY P. BLAIR, St. Louis
BARNEY BROOKS, Nashville
ELLIOTT C. CUTLER, Boston
WILLIAM E. GALLIE, Toronto
EVARTS A. GRAHAM, St. Louis
HOWARD C. NAFFZIGER, San Francisco
HARVEY B. STONE, Baltimore
ALLEN O. WHIPPLE, New York City

EDITORIAL BOARD

FREDERICK A. COLLER, Ann Arbor
EDWARD D. CHURCHILL, Boston
VERNON C. DAVID, Chicago
LESTER R. DRAGSTEDT, Chicago
RALPH K. GHORMLEY, Rochester, Minn.
ROSCOE R. GRAHAM, Toronto
SAMUEL C. HARVEY, New Haven
FRANK HINMAN, San Francisco
EMILE F. HOLMAN, San Francisco
EDWIN P. LEHMAN, University, Va.
FRANK L. MELENEY, New York City
JOHN J. MORTON, Rochester, N. Y.
THOMAS G. ORR, Kansas City, Kan.
WILDER G. PENFIELD, Montreal
ISIDOR S. RAVDIN, Philadelphia
MONT R. REID, Cincinnati
WILLIAM F. RIENHOFF, JR., Baltimore

COMMITTEE ON PUBLICATIONS

ARTHUR W. ALLEN
Boston, Mass.

CLAUDE S. BECK
Cleveland, Ohio.

ELEXIOUS T. BELL
Minneapolis, Minn.

ISAAC A. BIGGER
Richmond, Va.

ALBERT C. BRODERS
Rochester, Minn.

J. BARRETT BROWN
St. Louis, Mo.

ALEXANDER BRUNSCHWIG
Chicago, Ill.

LOUIS A. BUIE
Rochester, Minn.

WARREN H. COLE
Chicago, Ill.

C. D. CREEVY
Minneapolis, Minn.

GEORGE M. CURTIS
Columbus, Ohio

M. DE BAKEY
New Orleans, La.

JOHN STAIGE DAVIS
Baltimore, Md.

WILLIAM J. DIECKMANN
Chicago, Ill.

DANIEL C. ELKIN
Atlanta, Ga.

WILLIS D. GATCH
Indianapolis, Ind.

CHARLES F. GESCHICKTER
Baltimore, Md.

J. SHELTON HORSLEY
Richmond, Va.

J. MASON HUNDLEY, JR.
Baltimore, Md.

ANDREW C. IVY
Chicago, Ill.

DENNIS E. JACKSON
Cincinnati, Ohio

J. ALBERT KEY
St. Louis, Mo.

CHAUNCEY LEAKE
San Francisco, Calif.

FRANCIS E. LEJEUNE
New Orleans, La.

HAROLD I. LILLIE
Rochester, Minn.

JOHN S. LUNDY
Rochester, Minn.

FRANK C. MANN
Rochester, Minn.

CHARLES W. MAYO
Rochester, Minn.

GEORGE T. PACK
New York, N. Y.

ROBERT L. PAYNE
Norfolk, Va.

LEO G. RIGLER
Minneapolis, Minn.

ERNEST SACHS
St. Louis, Mo.

ARTHUR M. SHIPLEY
Baltimore, Md.

ALBERT O. SINGLETON
Galveston, Texas

MAURICE B. VISSCHER
Minneapolis, Minn.

RALPH M. WATERS
Madison, Wis.

JAMES C. WHITE
Boston, Mass.

PHILIP D. WILSON
New York, N. Y.

JOHN A. WOLFER
Chicago, Ill.

Vol. 14, No. 2, August, 1943. Surgery is published monthly by The C. V. Mosby Company, 3523 Pine Blvd., St. Louis (3), Mo. Subscription price: United States, its possessions, Pan-American Countries, $10.00 a year; Canada, $11.50 (Canadian Currency); Foreign, $11.00. Entered as Second-Class Matter January 20, 1937, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in U. S. A.

©CLB 601653

D&G SURGILON*

Sutures of Braided Nylon

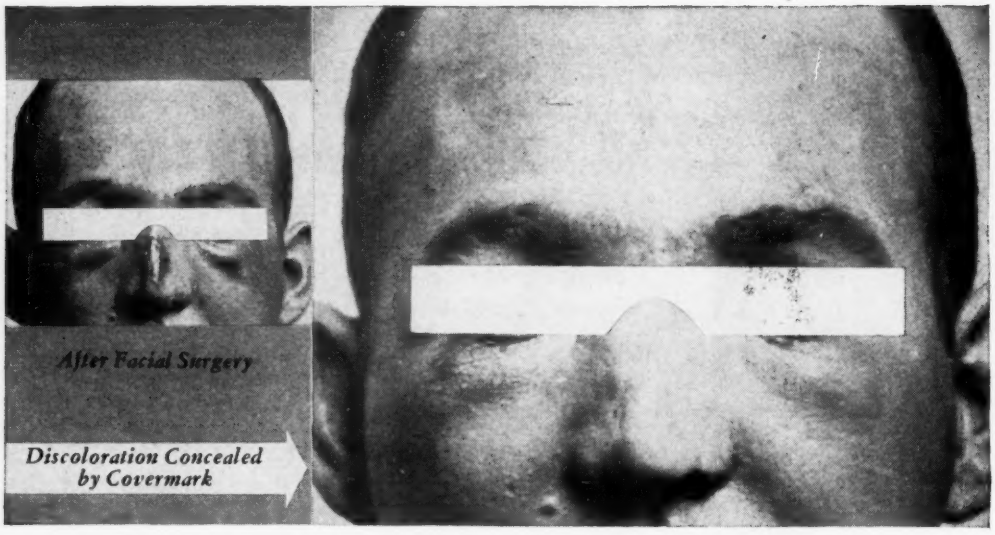
In order that the surgeon may have full opportunity to determine the clinical value of braided nylon under various circumstances and conditions, Surgilon has been made available in a range of sizes and use categories comparable to those of silk.

As is traditional of all D&G products, Surgilon reflects the high standard of technical craftsmanship attainable only through specialization. The exclusive D&G Anacap* process assures that Surgilon remains non-capillary both in the presence of tissue fluids and after repeated boiling or autoclaving.

* D&G REGISTERED TRADEMARK

DAVIS & GECK, INC.
BROOKLYN 1, NEW YORK

ARMY E NAVY



PSYCHOLOGICALLY IMPORTANT!

Covermark...
FOR POST-OPERATIVE SCARS

Conspicuous discoloration of post-operative scars on face and neck is often a serious mental handicap to the patient. That's why modern surgeons in military and civil practice are making wide use of Covermark during the healing period and in cases of permanent skin discoloration. Covermark completely, instantly, safely conceals birthmarks, X-ray burns, vitiligo, telangiectasis, liver spots and tattoo marks, as well as the discoloration of post-operative scars, varicose veins, lupus erythematosus, lupus vulgaris, psoriasis and other skin disorders.

Easy to apply—stays on all day or until intentionally removed—keeps the patient happily *un*selfconscious!

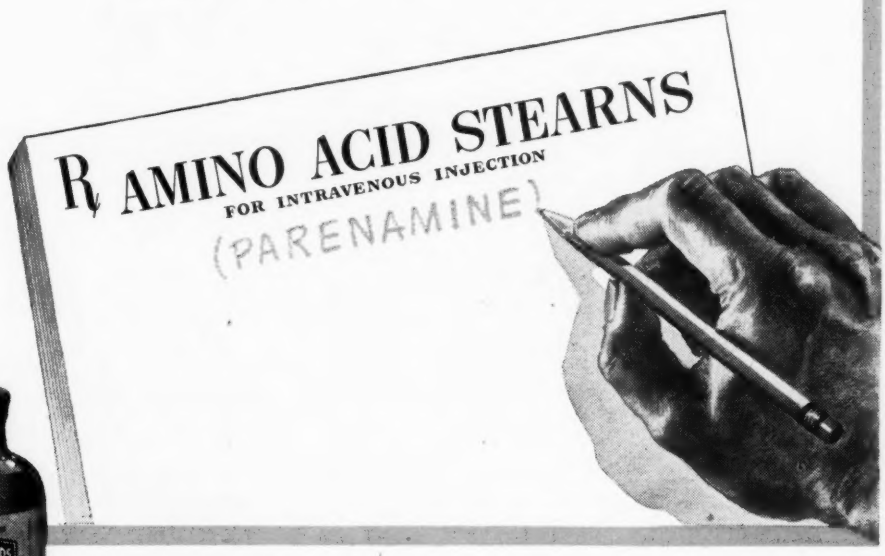
COVERMARK CREAM (*greaseless and waterproof—in all skin tones*) $3, $1.25
COVERMARK SPOT-STIK (*light, medium, dark, suntan and brunette*) $1.25

Write for literature

Professional Service Department
LYDIA O'LEARY, INC.
551 Fifth Avenue, New York
30 N. MICHIGAN AVENUE, CHICAGO

An Added Safeguard Against Confusion

A New Registered Name



Now, to make doubly sure that you will obtain exactly what you require when you specify parenteral amino acids, Stearns has registered the trade name "Parenamine" as additional identification of Amino Acids Stearns—the first effective parenteral substitute for protein alimentation.

And here is more news about this widely discussed contribution to pre- and post-operative care and to the study and treatment of nutritional deficiencies: steadily increasing production assures that hospitals, clinics and individual physicians will soon be receiving enough to meet present requirements. Moreover, because demand continues to grow at an increasing rate, Stearns is already planning greater production facilities.

Frederick Stearns *& Company*

Since 1855... ESSENTIALS OF THE PHYSICIAN'S ARMAMENTARIUM

NEW YORK KANSAS CITY SAN FRANCISCO WINDSOR, ONTARIO **DETROIT, MICH.** SYDNEY, AUSTRALIA AUCKLAND, NEW ZEALAND

NOW.. ANTISEPTIC COSTS LOWERED AS MUCH AS 80%

New Concentrate Makes Surgical Germicide for 40c a G[illegible]lon

A development of utmost importance to every physician and surgeon is this new concentrate for preparing antiseptic solutions and tinctures for surgical use—

CEEPRYN

Brand of Cetylpyridinium Chloride

CONCENTRATED SOLUTION

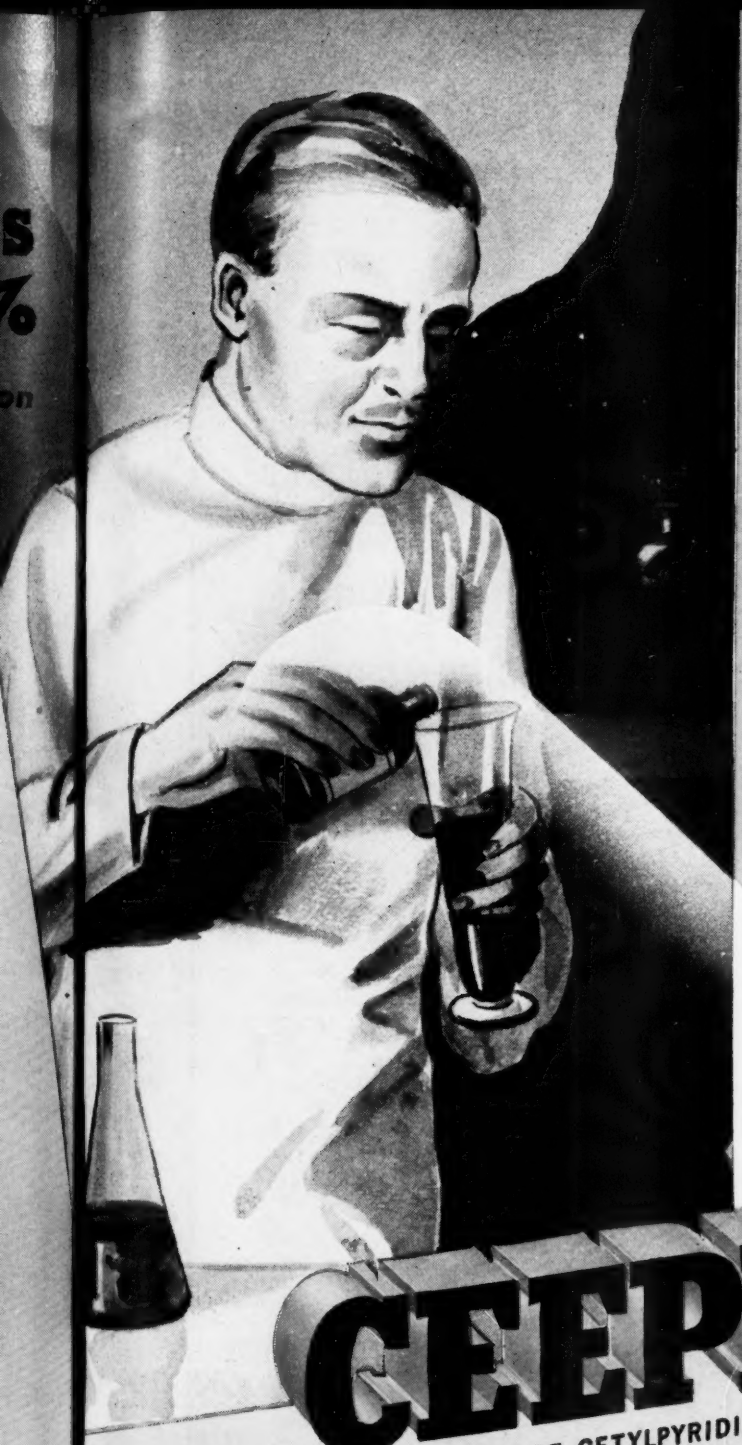
The new product is a 10.56% solution of Ceepryn, quaternary ammonium salt germicide which is well known for its potent and non-selective bactericidal action, penetrating ability, unique detergent property, and exceptionally low tissue toxicity.

By using Ceepryn Concentrated Solution, antiseptic tinctures and solutions can be prepared by the hospital at costs which represent tremendous savings when compared with prices formerly paid for surgical germicides, for example:

AQUEOUS SOLUTIONS — *Cost per Gallon*	
Ceepryn (1:1000) prepared from concentrate	$ .40
Another non-mercurial antiseptic (1:1000)	$5.00
A representative mercurial antiseptic (1:1000)	$6.24
TINCTURES — *Cost per Gallon*	
*Ceepryn (1:500) prepared from concentrate	$1.46
*Ceepryn (1:200) prepared from concentrate	$2.66
Another non-mercurial antiseptic (1:1000)	$6.25
A representative mercurial antiseptic	$7.02
Another representative mercurial antiseptic (1:200)	$21.24
Tincture Iodine (7%)	$4.50

* *Ceepryn tincture costs based on tax-free alcohol (available at most large hospitals) at 65c per gallon and acetone at $2.60 per gallon.*

THE WM. S. MERRELL COMPANY



Ceepryn Concentrated Solution is easy to use. Aqueous solutions are made simply by diluting with the required quantity of distilled water; tinctures by diluting with distilled water, alcohol and acetone. Tinctures may be tinted by adding the special Ceepryn Color Solution available for this purpose. Full directions and formula tables are on the package.

Ceepryn Concentrated Solution is supplied in 180 cc. bottles which can be purchased by hospitals at $2.00 each. Ceepryn Color Solution is offered in 30 cc. bottles at $1.00 each. Also available for office use from your druggist at slightly higher cost.

Specify CEEPRYN for surgical preparation of your patients

CEEPRYN

BRAND OF CETYLPYRIDINIUM CHLORIDE

CONCENTRATED SOLUTION

MERRELL

115th Year

Trade Mark "Ceepryn" Reg. U. S. Pat. Off.

Founded 1828 • Cincinnati, U. S. A.

SURGERY

Editors: ALTON OCHSNER, M.D., 1430 Tulane Ave., New Orleans, La., and OWEN H. WANGENSTEEN, M.D., University Hospitals, Minneapolis, Minn.

Associate Editor: ALFRED BLALOCK, M.D., Johns Hopkins Hospital, Baltimore, Md.

Published by THE C. V. MOSBY COMPANY, 3525 Pine Blvd., St. Louis (3), U.S.A.

Great Britain Agents: Henry Kimpton, Ltd., 26 Bloomsbury Way, London, W.C.1.
Entered at the Post Office at St. Louis, Mo., as Second-Class Matter.

Published Monthly. Subscriptions may begin at any time.

Editorial Communications

Original Communications.—This Journal invites concise original articles of new matter in the broad field of clinical and experimental surgery. Descriptions of new techniques and methods are welcomed. Articles are accepted for publication with the understanding that they are contributed solely to SURGERY.

Manuscripts submitted for publication may be sent to Dr. Alton Ochsner, 1430 Tulane Avenue, New Orleans, Louisiana, or to Dr. Owen H. Wangensteen, University Hospitals, Minneapolis, Minnesota.

Neither the editors nor the publishers accept responsibility for the views and statements of authors expressed in their communications.

Translations.—Manuscripts written in a foreign language, if found suitable for publication, will be translated without cost to the author.

Manuscripts.—Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. References should be placed at the end of the article and should conform to the style of the Quarterly Cumulative Index Medicus; viz., name of author, title of article, and name of periodical with volume, page, and year. Illustrations accompanying manuscripts should be numbered, provided with suitable legends, and marked on margin or back with the author's name.

Authors should indicate on the manuscript the approximate position of text figures. The original drawings, not photographs of them, should accompany the manuscript.

Illustrations.—A reasonable number of half-tone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the editors for color plates, elaborate tables or extra illustrations. Copy for zinc cuts (such as pen drawings and charts) should be drawn and lettered only in India ink, or black typewriter ribbon (when the typewriter is used), as ordinary blue ink or colors will not reproduce. Only good photographic prints or drawings should be supplied for half-tone work.

Exchanges.—Contributions, letters, exchanges, reprints, and all other communications relating to SURGERY should be sent to one of the editors.

Review of Books.—Books and monographs, native and foreign, will be reviewed according to their merits and as space permits. Books may be sent to Dr. Owen H. Wangensteen, University Hospitals, Minneapolis, Minn.

Reprints.—Reprints of articles published among "Original Communications" must be ordered directly through the publishers, The C. V. Mosby Co., 3523 Pine Blvd., St. Louis (3), U. S. A., who will send their schedule of prices.

Business Communications

Business Communications.—All communications in regard to advertising, subscriptions, change of address, etc., should be addressed to the publishers, The C. V. Mosby Company, 3523 Pine Blvd., St. Louis (3), Mo.

Subscription Rates.—Single copies, 85 cents. To any place in the United States and its Possessions and the Pan-American Countries, $10.00 per year in advance. To Canada, $11.50 (Canadian Currency), and under foreign postage, $11.00. Includes two volumes a year, January and July.

Remittances.—Remittances for subscriptions should be made by check, draft, post office or express money order, or registered letter, payable to the publishers, The C. V. Mosby Co.

Change of Address.—The publishers should be advised of change of subscriber's address about fifteen days before the date of issue, with both new and old addresses given.

Nonreceipt of Copies.—Complaints for nonreceipt of copies or requests for extra numbers must be received on or before the 10th of the month preceding publication; otherwise the supply is likely to be exhausted.

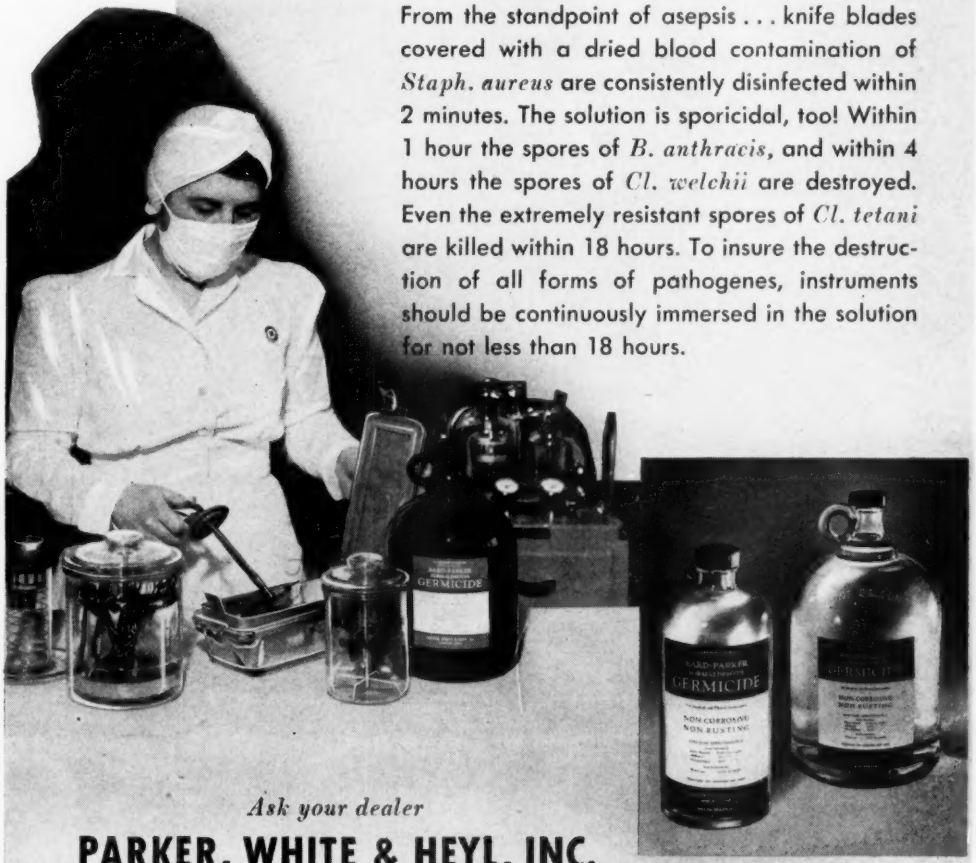
Advertisements.—Only articles of known scientific value will be given space. Forms close tenth of month preceding date of issue. Advertising rates and page sizes on application.

Protecting inherent qualities of instruments...secondary only to asepsis

Bard-Parker Formaldehyde Germicide

not only provides high germicidal potency—prolonged immersion of delicate steel instruments will not result in rust or corrosive damage. Obviously, the functional efficiency of any instrument depends upon such protection of its inherent factory qualities during the sterilizing process.

From the standpoint of asepsis . . . knife blades covered with a dried blood contamination of *Staph. aureus* are consistently disinfected within 2 minutes. The solution is sporicidal, too! Within 1 hour the spores of *B. anthracis*, and within 4 hours the spores of *Cl. welchii* are destroyed. Even the extremely resistant spores of *Cl. tetani* are killed within 18 hours. To insure the destruction of all forms of pathogenes, instruments should be continuously immersed in the solution for not less than 18 hours.



Ask your dealer

PARKER, WHITE & HEYL, INC.

DANBURY, CONNECTICUT

A BARD-PARKER PRODUCT

Bottleneck . . . or MILLRACE

THROUGH the cutting edge of his surgical blade must flow all the operator's skill—either with bottleneck difficulty . . . or with the freedom and controlled power of a millrace.

Crescent blades help transmit high surgical potential into brilliant surgical achievement, since—

First—The cutting edge is ground on a longer, more acute bevel—*for sharpness.*

Second—One-third more of the finest steel is built into every blade—*for rigidity.*

Third—This weight is distributed evenly, without thinning down from the back—*for balance.*

With this extra degree of rigidity, balance, and sharpness at his disposal, the surgeon's mind can "race" ahead with sure confidence in his hand's ability to keep unfaltering pace.

Your surgical dealer will provide liberal samples of these superior blades . . . or write to

CRESCENT SURGICAL SALES CO., INC.
New York, N. Y.

Fit all standard handles

Crescent

SURGICAL BLADES AND HANDLES

THE MASTER HAND DESERVES A MASTER BLADE

A DECADE OF UNIFORMITY...DIGIFOLIN

DIGIFOLIN* maintains the same potency in which it has been available for over a decade. While official digitalis preparations according to U. S. P. XII will be somewhat weaker than those made according to U. S. P. XI, they will still be stronger than prior to 1936.

Thanks to its uninterrupted constancy, DIGIFOLIN, as heretofore, will enable the physician to prescribe a constant potent preparation of purified digitalis glucosides in tablets, ampuls or solution.

DIGIFOLIN HAS NOT CHANGED

*Trade Mark Reg. U. S. Pat. Off.

CIBA *Pharmaceutical Products, Inc.*
SUMMIT, NEW JERSEY

GROWING UP WITH THE NATION

In 1876, the Philadelphia Centennial heralded the approach of the great industrial era. In the same city, a youthful organization was implanting its roots in the soil of American pharmacy. William Richard Warner, true to the pioneering spirit of his age, was even then evolving new and better methods of making medicinal drugs.

Over the years, the house of William R. Warner & Co., Inc. has grown until today its branches girdle the globe, in fulfillment of its early chosen motto, "Omnis Orbis." And, conscious of its obligation to play a worthy part in the progress of pharmaceutical science, the house of Warner, through its affiliated Warner Institute for Therapeutic Research, continues to pioneer in the pursuit of original investigation and research, to the end that still better, safer means may be found for the prevention and control of disease.

OMNIS ORBIS
WARNER
ESTABLISHED 1856

WILLIAM R. WARNER & CO., INC.

113 West 18th Street, New York • 404 South Fourth Street, St. Louis

Branches and Agencies in 75 foreign countries

ETHICON SUTURE "FUTURES"

NO. II

THE TRANS-ILLUMINATED FIELD . . . Forecast for the future is a new method of lighting for surgery, with complete illumination of the operative field, enabling the surgeon to see a three-dimensional area clearly. Shadows and glare would be eliminated. The circulation in the tissues and organs would be observable throughout the operation. For modern advancements in suture making see following pages. ➡

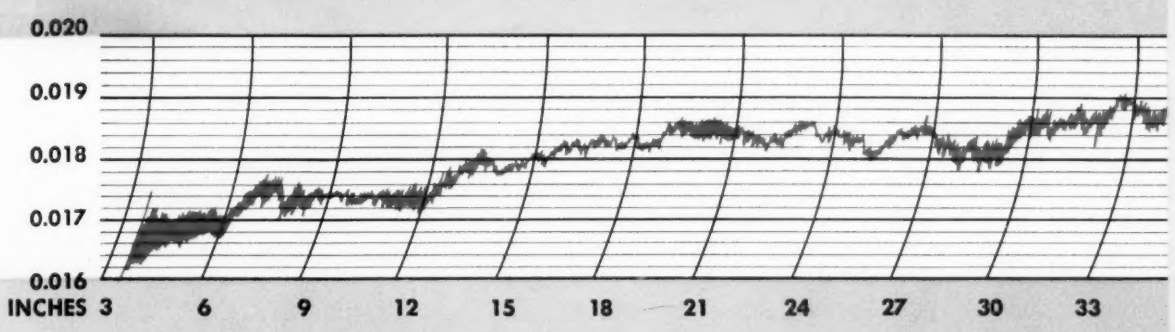
Now four scientific developments improve catgut sutures

● Johnson & Johnson is proud to present the new Ethicon, which embraces four scientific improvements in suture making. It has greater uniformity of gauge and strength, minimizes knot breakage, a Lock-Knot Finish which gives greater security of knots, and Tru-Chromicizing, which controls digestion. Today the Ethicon label is your assurance of the finest quality catgut, the accomplishment of years of research, rigid laboratory control and exclusive manufacturing methods.

Take advantage of these four improvements that aid in locking your knots—specify Ethicon.

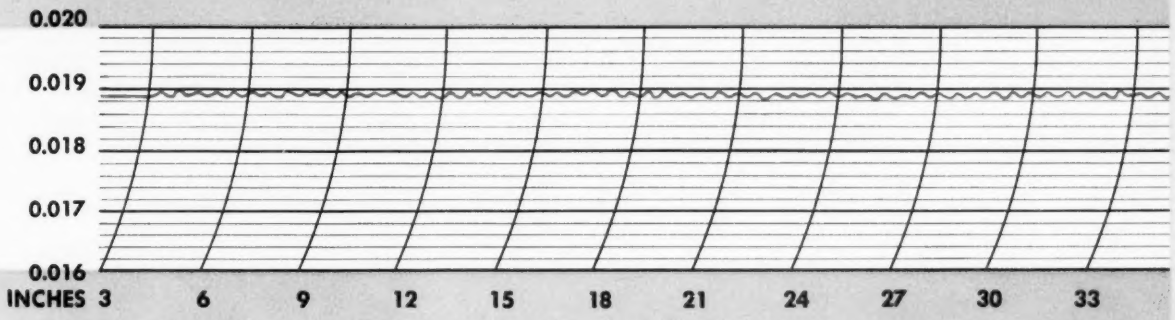
EXCLUSIVE—TRU-CHROMICIZING RESISTS PREMATURE ABSORPTION

Many sutures are chromicized merely on the surface. The chromic coating is easily abraded, exposing untreated catgut, hastening disintegration. Ethicon's exclusive through-and-through chromicizing resists premature absorption.



ORDINARY SUTURE

SIZE 1, charted by the phctoelectric microgauge, shows diameter irregularities along entire length of strand.



ETHICON SUTURE

SIZE 1, charted in same manner by the microgauge, shows gauge-uniformity resulting from exclusive Tru-Gauging process. This gauge-uniformity assures greater strength by eliminating "low spots" that cause weakness.

ETHICON

LOCK KNOT

SUTURES

Johnson & Johnson

ETHICON
SUTURES

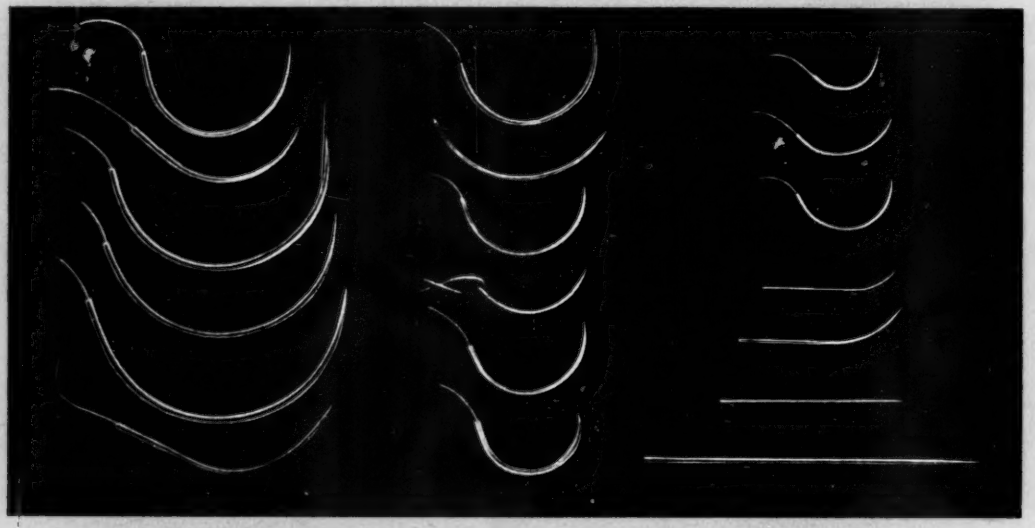
SUTURES FOR EVERY SURGICAL FIELD

Ethicon Absorbable and Non-Absorbable Sutures are supplied in a wide range of materials to meet the needs of every surgical field.

General Surgery
Gynecology
Obstetrics
Gastro-Intestinal
Urology

Eye Surgery
Dental
Ear, Nose, Throat
Thyroid
Neuro-Surgery

Plastic Surgery
Orthopedics
Oral Surgery
Proctology
Industrial Surgery



A few of the many Ethicon Needles

The above needles are a few of the many special needles attached to Ethicon Sutures. Supplied with either catgut or non-absorbable material, Ethicon Atraloc Needles (non-traumatic type) are firmly and smoothly swaged to the suture. These needle-suture combinations speed up your work and minimize trauma.

Johnson & Johnson

World's Largest Manufacturer of Surgical Catgut

Suture Laboratories at
New Brunswick, N. J.; Chicago, Ill.;
Brazil; Argentina; England; Australia.

Ethicon Suture Division
Johnson & Johnson, New Brunswick, N. J.

☐ Please send me the new Ethicon Suture Catalog.

☐ Please have an Ethicon Suture consultant call on me.

*Name*_____

*Address*_____

For Victory - Freedom - Life

UNENDING battles are going on within the great battles that rage throughout the globe — but these are battles for life, not death. Arms borne by our military surgeons are modern drugs and surgical instruments of the finest type. A goodly percentage of these instruments carry the name of Sklar—trusted the world over during peace, and now fulfilling their purpose in the skilled hands of surgeons attached to every branch of our armed services.

J. SKLAR MANUFACTURING COMPANY
LONG ISLAND CITY, N. Y.

War demands have limited the instruments available for civilian use. We shall continue to do our best to supply essential civilian requirements. But for safety's sake, care well for the instruments you now have —make them last as long as possible.

WITH THE ARMORED DIVISIONS

LINN BAIL

Woman's work

EVERYWHERE women are carrying a wartime load —the doctor's wife with absent spouse—the nurse doing double duty while her colleague serves in a foreign land—the girl who does a man's work in industry to free another fighter for the United Nations.

In times like these the Lilly tradition of quality is appreciated more than ever by those who are responsible for Lilly products. Meticulous methods of standardization, production, and inspection are so much a part of the Lilly structure that new workers quickly sense their obligation to carry on no less efficiently than the men they have replaced.

ELI LILLY AND COMPANY • INDIANAPOLIS, INDIANA, U. S. A.

SURGERY

VOL. 14 AUGUST, 1943 NO. 2

Original Communications

A CONSIDERATION OF THE NONOPERATIVE TREATMENT OF CARDIAC TAMPONADE RESULTING FROM WOUNDS OF THE HEART

ALFRED BLALOCK, M.D., AND MARK M. RAVITCH, M.D., BALTIMORE, MD.
(From the Department of Surgery of the Johns Hopkins Medical School and Hospital)

ALTHOUGH it is rather generally agreed that the treatment of wounds of the heart, with resulting tamponade, should consist of pericardiotomy with suture of the wound, aspiration instead of open operation has been suggested by several surgeons. Felsenreich[1] stated that the treatment of penetrating wounds of the ventricles of the heart should be by operation, whereas wounds of the auricle should be treated by nonoperative means. This distinction is made because of the smaller pressure in the auricles as compared with the ventricles and the greater likelihood of cessation of bleeding into the pericardium from a wound of the auricle. Singleton[2] reported ten patients with wounds of the heart; one of them, in whom a shot lodged in the right ventricle, was treated successfully by aspiration alone. Singleton stated: "Therefore, we are of the opinion that prevention or relief of 'Herz tamponade' will save life in a certain number of heart injuries. This may be done for temporary relief, giving time for operative intervention in some cases, and occasionally aspiration alone results in recovery as in the case reported." Several years ago Bigger[3] described the results of operations on seventeen patients with wounds of the heart. He stated: "In the past we have been inclined to operate upon all patients with signs of tamponade or with signs of cardiac injury and moderate or massive intrapleural hemorrhage. As a result of our experience and a review of the literature we now believe that patients with heart wounds should be operated upon promptly if the indications are clear and urgent, but if the indications are not urgent some form of conservative treatment should be considered." Specific suggestions were made by Bigger as to the nature of the nonoperative treatment.

Received for publication, Nov. 2, 1942.

In discussing this paper, Elkin[4] reported the death of a patient three weeks after the receipt of a wound of the heart, the patient having been treated by nonoperative means. Necropsy showed that death resulted from rupture of a traumatic aneurysm of a coronary artery. Strieder[5] reported a case of a stab wound of the heart in which aspiration of the pericardial cavity was carried out and the patient had an uneventful convalescence. He warns, however, that "not operating upon a patient with a stab wound of the heart is a very hazardous course to follow." In a recent paper, Elkin[6] says that operation should be carried out as soon as the diagnosis is established. In a personal communication, Dr. Turner of the Meharry Hospital in Nashville informs us that recovery has followed the nonoperative treatment of two of his patients with stab wounds of the heart.

The reported mortality rate[3] from wounds of the heart which have been treated by operative means is approximately 50 per cent. Most of the deaths have been ascribable to the effects of the injury itself, but a good many are due to untoward incidents during the operative procedure or to complications which followed the operation. The question arises as to whether the mortality rate would be reduced if nonoperative treatment was used in those instances in which a rapid reaccumulation of blood does not ensue following paracentesis.

The present communication consists of a report of several cases of wounds of the heart in which nonoperative treatment was employed. These cases are similar to a number of others which have been observed.

CASE REPORTS

The first case report presents an example of recovery from what was apparently a stab wound of the heart, neither aspiration nor operation being employed. A slow, favorable response followed the administration of blood plasma.

CASE 1.—G. W. (J. H. H. No. 255213), a colored man, aged 28 years, was carried into the Accident Room at 3:30 A.M. on March 21, 1942, after having been stabbed at 3:20 A.M. On arrival he was unconscious, cold, perspiring profusely, and restless; the pulse could not be felt. The veins were engorged, the blood pressure was unobtainable, the heart sounds were muffled, and the second sound was inaudible at the base. There was a small stab wound in the third interspace to the left of the sternum. Venous pressure as obtained in an antecubital vein was 230 mm. of water. On fluoroscopic examination there was found to be almost complete absence of pulsations of the heart. There was no evidence of an accumulation of blood in either of the pleural cavities. An intravenous infusion of 250 c.c. of human blood plasma was given shortly after admission. The patient recovered consciousness soon after. The pulse was palpable and the systolic arterial pressure rose to 40 mm. of mercury. By 5 A.M., which was a little more than one hour after admission, the venous pressure was 255 mm. of water and the pulse was stronger.

The patient was taken to the operating room. It was observed on his arrival there that the systolic pressure was 70 mm. of mercury and the pulse had improved in quality. It was decided that further observation was indicated. There was a

slowly progressive rise in the arterial pressure to 90 mm. of mercury, and the patient was sent to the ward without operation. He was conscious, the skin was dry, and the quality of the pulse was improved, the rate being 88 per minute. An x-ray film of the chest which was taken twelve hours after the injury showed "an increase in the transverse diameter of the heart due chiefly to enlargement of the left ventricular shadow." Twenty-four hours after admission the patient's temperature was 101° F. and the administration of sulfadiazine was begun. The heart sounds were heard with ease and the lungs appeared clear. There was no indication of air or blood in the pleural cavities. The report of an electrocardiographic examination twenty-four hours after admission was as follows: "Normal sinus rhythm. Normal axis. T I and T II and T4F upright. T III upright but low. Marked elevation of S-T I, II and 4F. Initial upward deflection in chest lead. Changes suggest hemopericardium or pericarditis and have been noted in other cases with stab wounds of the heart."

The patient was permitted to sit up on the sixth day after the injury since he had been afebrile for three days and was asymptomatic. He was discharged from the hospital nine days after the injury. He was last seen one month after discharge from the hospital and then complained of shortness of breath on exertion, which was relieved by rest. The physical examination was negative. On x-ray examination the heart and aorta were seen to be normal. An electrocardiographic examination showed T I still inverted.

Comment.—The patient was admitted in apparently desperate condition, but recovered with the administration of human plasma. Fluoroscopic examination, venous pressure determination, and electrocardiographic studies supported the clinical impression of intrapericardial hemorrhage.

The second case presents an example of the treatment of a patient with a wound of the heart by aspiration and the administration of fluids intravenously, an operation not being performed.

CASE 2.—N. J. (J. H. H. No. 262265), a colored man, aged 48 years, was carried into the Accident Room at 2:25 A.M. on June 6, 1942, about ten minutes after he had been stabbed in the chest. The wound was 3 cm. in length and was located in the third interspace to the left of the sterum. At first glance he was thought to be dead, and the surgical intern who was engaged in attending to other patients requested a medical intern to pronounce the patient "dead on arrival." It was found, however, that faint heart sounds could be heard. The patient was unconscious, cold, and pulseless, and the blood pressure was unobtainable. Glucose-saline solution was administered intravenously in the amount of 100 c.c., and this was followed by the giving of unmatched Group O blood from the blood bank. While the blood was being administered the pericardial cavity was aspirated in the fourth interspace to the left of the sternum, and 30 c.c. of blood were removed. The response was dramatic; the patient stopped perspiring and became violently restless, showing considerable strength. Twenty-five minutes after the patient's admission the pulse became easily palpable and the blood pressure was obtained at 90/60 mm. of mercury. On fluoroscopic examination the pulsations of the heart were visible but diminished. Approximately thirty minutes after the patient was first seen the venous pressure was 170 mm. of water. Physical signs and x-ray examination demonstrated hemothorax in the left pleural cavity. An electrocardiographic examination was carried out about fifteen hours after the admission of the patient. The report was as follows: "Normal sinus rhythm. Normal axis. Intraventricular conduction time is prolonged. S I is very prominent and broad. T I and II are upright. T III is sharply inverted. T4F is diphasic. The record is characteristic of tracings associated with acute pericarditis."

A small amount of bloody fluid was aspirated from the left pleural cavity and was found to be sterile. The evidence of pleural fluid disappeared in a week. The patient was discharged from the hospital seventeen days after admission.

Comment.—The patient was at the point of death on admission. His condition improved dramatically following the aspiration of only 30 c.c. of blood from the pericardial sac and after the administration of blood intravenously. Convalescence was uneventful.

It is important to appreciate the fact that a prolonged period of low blood pressure and inadequate blood flow may result in serious complications if not in irreparable damage. Edward S. Stafford observed and reported[7] a case in which acute renal failure developed as a result of cardiac tamponade which was not recognized until twelve hours after the injury of the heart. An abbreviated account of this case follows.

CASE 3.—J. S. (J. H. H. No. 165590), a colored man, aged 27 years, entered the hospital at 9:15 P.M. on March 11, 1939. He had been stabbed shortly before in the second left intercostal space. His clothes were bloodsoaked and the radial pulses were imperceptible. He was considered to have a wound of one of the great vessels at the base of the heart. He was given glucose solution intravenously and the systolic blood pressure rose to 60 mm. of mercury. It remained between 60 and 80 mm. of mercury throughout the night. The following morning, twelve hours after admission, the pulse and blood pressure were unobtainable. The venous pressure was 200 mm. of water. Cardiac tamponade was suspected and aspiration of the pericardial sac yielded 140 c.c. of dark blood. The systolic blood pressure rose immediately to 90 mm. of mercury and the venous pressure declined to 100 mm. of water. Despite a total fluid intake of more than eight liters in the first twenty-four-hour period, the patient did not void and the bladder was not distended. The following day the blood pressure was 146/96 mm. of mercury, and it remained at essentially this level during the rest of his stay in the hospital.

On the fourth day after admission the nonprotein nitrogen was 148 mg. per cent and the volume of urine was small. Urine examination showed erythrocytes, leucocytes, casts, and albumin. Glucose solution was administered intravenously and a retention catheter was inserted into the bladder. The patient continued for several days to show signs of renal failure. The nonprotein nitrogen rose to 220 mg. per cent and the excretion of phenolsulphonephthalein in two hours was only 17 per cent. A few days later the patient began to improve, and there was no evidence of residual renal damage on discharge from the hospital forty-one days after the injury.

Comment.—The experience with this patient, who had cardiac tamponade for twelve hours before it was recognized and in whom acute renal failure developed, emphasizes the importance of prompt recognition and treatment of tamponade. Aspiration of the pericardium resulted in relief of the tamponade and an operation was unnecessary. The acute renal failure probably would not have occurred had the aspiration been performed soon after the patient's admission to the hospital.

The following case report presents an example of a patient with a wound of the heart who was treated by aspiration of the pericardial cavity and by open operation. The condition found at operation indicated that the patient would probably have survived even though this procedure had not been carried out.

CASE 4.—J. W. (J. H. H. No. 252711), was a colored man, aged 17 years. Supported by two friends, the patient was admitted into the Accident Room at 11:15 P.M. on Feb. 17, 1942. He collapsed on arrival. The pulse was palpable at first but then became imperceptible. The heart sounds were audible but suppressed. The peripheral veins were distended. There was a stab wound in the fifth interspace to the right of the sternum. Pericardial aspiration was carried out at once and yielded 60 c.c. of dark blood. This procedure was immediately followed by improvement in the pulse and return of consciousness. The intravenous administration of fluids was begun and the patient was taken to the operating room.

Twenty-five minutes after the patient's arrival in the Accident Room a left parasternal incision was made. The pericardium was exposed and opened. In the pericardial cavity there was only a blood clot of moderate size which conformed to the shape of the heart and pericardium. A wound 1 cm. in length was seen near the apex of the heart. There was no active bleeding. It was closed with a single silk suture, and the incision in the chest was closed. A perforation of the left pleura, made at operation, was repaired. The patient was given whole blood plasma and glucose-saline solution during the operative procedure. His condition at the end of the operation was good.

Tension pneumothorax developed on the right side following the operation; this was relieved by repeated aspirations and finally by the insertion of a needle which was left in place for twenty-four hours. Twelve hours after admission the patient's temperature was 103.6° F., and sulfadiazine was administered. The temperature and pulse remained elevated for three days and then dropped abruptly. The subsequent convalescence was smooth. The patient was discharged from the hospital sixteen days after admission.

Comment.—The patient responded dramatically to pericardial aspiration. He was not kept under further observation, however, but was taken to the operating room and the pericardial cavity was opened. The pericardium was found to be empty of blood save for a single clot, and the wound in the heart was not bleeding. It seems likely that aspiration alone would have accomplished the desired result and that an operation was unnecessary.

DISCUSSION

Many patients with heart wounds succumb as a result of hemorrhage very soon after the injury. The mortality rate in those reported cases in which the patients reached a hospital and were operated upon is almost 50 per cent. The mortality rate is high even in the hands of those who have performed a number of such operations, and it is likely that the rate is considerably higher when the procedure is carried out by persons of less experience. It is well to remember that isolated unsuccessful cases are usually not reported.

The question arises whether the sum total of successful end results will not be greater if a more conservative policy in regard to immediate operation is adopted in those instances in which there is not active bleeding through the chest wound or into the pleural cavity. In other words, is one not warranted in delaying operation and in using nonoperative means, including aspiration, in those instances in which the patient's symptoms are due to tamponade rather than to continued active bleeding? If a positive answer to this question is the correct one, it is nevertheless important to realize that all facilities should be available for immediate operation if it becomes necessary and that

there is a limit to the length of time (probably two hours) that tamponade may be allowed to persist. If blood reaccumulates rapidly following aspiration, it is agreed that exposure and suture of the heart wound is indicated. If more than one aspiration is necessary, one should allow at least fifteen minutes between paracenteses in order that the chances of closure of the would by a clot may be increased. If one has good reason to believe an auricle rather than a ventricle has been injured, one may more safely defer operation.

The observations and opinions which are expressed here support the directions[8] prepared recently for medical officers in the U. S. Army by E. A. Graham, I. A. Bigger, E. D. Churchill, and Leo Eloesser. These directions refer to the treatment of penetrating heart wounds with resulting tamponade and are as follows:

"(a) Aspirate the blood from the pericardium by the costoxiphoid route, if possible.

"(b) Repeat if there is a recurrence.

"(c) If it again recurs, perform a cardiorrhaphy through an extrapleural exposure."

It is to be emphasized that our paper deals with the treatment of heart wounds with associated cardiac tamponade rather than those in which there is continued bleeding into the pleural cavity or through the opening in the chest wall. It is obvious that an operation is necessary in those instances in which active bleeding continues.

REFERENCES

1. Felsenreich, F.: Konservative oder operative Therapie bei Vorhofsverletzungen des Hersens, Arch. f. klin. Chir. **166**: 694-703, 1931.
2. Singleton, A. O.: Wounds of the Heart and a Discussion of the Causes of Death, Am. J. Surg. **20**: 515-541, 1933.
3. Bigger, I. A.: Heart Wounds, J. Thoracic Surg. **8**: 239-253, 1939.
4. Elkin, D. C.: Discussion of article by Bigger.[3]
5. Strieder, J. W.: Stab Wound of the Heart, J. Thoracic Surg. **8**: 576-577, 1939.
6. Elkin, D. C.: The Diagnosis and Treatment of Cardiac Trauma, Ann. Surg. **114**: 169-185, 1941.
7. Stafford, E. S.: Renal Failure as a Complication of Cardiac Tamponade, J. Thoracic Surg. **9**: 652-655, 1939.
8. United States War Department: Guides to Therapy for Medical Officers (March 20, 1942). P. 185. Technical Manual 8-210. Washington, D. C.

NONPENETRATING ABDOMINAL TRAUMA

EMERSON CROSBY KELLY, M.D., ALBANY, N. Y.
(From the Department of Surgery, Albany Hospital and Albany Medical College)

THIS review of the incidence and mortality rate of nonpenetrating abdominal trauma covers a period of fifteen years from Jan. 1, 1927, to Dec. 31, 1941, at the Albany Hospital, a general hospital of about 600 beds, which receives the usual proportion of highway, home, and industrial accidents. Approximately 30 per cent of admissions are to the surgical service. A study of nonpenetrating abdominal trauma in this institution should, therefore, indicate the frequency and seriousness of these injuries.

The number of admissions at the Albany Hospital has steadily increased from 6,848 in 1927, to 13,229 in 1941. The total number for this period was 157,344. Of this total, 74 patients had nonpenetrating abdominal trauma. They were distributed among 21 doctors. Hence, most of the doctors saw very few patients with this type of injury and there was no uniformity in treatment. Thirty-three of these patients died. The mortality rate for this type of injury was therefore 44 per cent.

For comparison with other serious traumas, during the same period 269 patients or approximately 0.17 per cent of the total number were admitted with fractures of the vertebrae, and 207 patients or approximately 0.13 per cent with fracture of the pelvis.

It is therefore apparent that nonpenetrating abdominal trauma is infrequent but has a very high mortality rate.

Table I shows the type of lesion with the number of patients who died or recovered and the mortality percentage. Table II also shows the type of lesion year by year and reveals that a specific type of lesion may be found only at intervals of several years. Table III gives the type of injury received and shows that 55 per cent of the patients were injured as the result of automobile accidents. Table IV gives the time of operation after the injury was received. Fifty of the seventy-four patients were not operated on, either because their condition was in extremis on admission or because they improved under expectant treatment, which occurred most frequently in cases of contusions of the kidney. In this small series of so many different types of trauma a figure giving deaths in relation to time of operation would be of no value. Table V shows time of death after the patient was injured; almost half the patients died within the first twenty-four hours.

Received for publication, Dec. 17, 1942.

TABLE I

TYPE OF LESION

	TOTAL	DIED	RECOVERED	DIED (PER CENT)
Bladder	5	3	2	60
Intestine	13	9	4	69
Kidney	29	3	26	10
Liver	16	12	4	75
Mesentery	1	0	1	0
Spleen	9	5	4	55
Stomach	1	1	0	100
	74	33	41	44

TABLE II

TYPE OF LESION BY YEARS

YEAR	BLADDER	INTESTINE	KIDNEY	LIVER	MESENTERY	SPLEEN	STOMACH
1927				2 D			
1928		1 D	1 L				
1929			1 L				
1930	1 L	1 D	1 L				
			1 D				
1931		1 L	1 L	1 L		1 D	
				1 D			
1932			2 L	1 D			
			2 D				
1933	1 D	2 D				1 D	
1934	1 D		4 L	3 D		3 D	
1935	1 D	1 D	1 L	3 D			
1936		2 L	4 L	1 D			
		2 D					
1937			3 L	1 D			
1938			1 L			2 L	
1939		1 L	1 L	2 L		1 L	1 D
		1 D					
1940	1 L	1 D	3 L	1 L	1 L		
1941			3 L			1 L	
Total	2 L	4 L	26 L	4 L	1 L	4 L	1 D
	3 D	9 D	3 D	12 D		5 D	

D, died.
L, lived.

TABLE III

TYPE OF INJURY

	BLADDER	INTESTINE	KIDNEY	LIVER	MESENTERY	SPLEEN	STOMACH	TOTAL
Fall	2	1	8	3	1	1		16
Blow		8	4	1		2	1	16
Hit by vehicle	1	2	7	6		4		20
Driving automobile	1		1	2				4
Riding in automobile	1	1	9	4		2		17
Taxis on hernia		1						1
								74

Total number due to automobiles 41, or 55 per cent.

TABLE IV

TIME OF OPERATION

AFTER INJURY

TIME	NO.
Within 6 hr.	10
Within 12 hr.	7
Within 24 hr.	3
Over 24 hr.	4
No operation	50
Total	74

TABLE V

TIME OF DEATH

AFTER INJURY

TIME	NO.
Within 1 hr.	3
Within 24 hr.	12
Within 48 hr.	8
Within 1 wk.	6
Over 1 wk.	4
Total	33

Bladder.—Only five patients with rupture of the urinary bladder were admitted. The one patient who had no associated injuries was a 60-year-old man who fell while intoxicated and died within twenty-four hours. The cause of death was given as peritonitis but in view of the short history, some associated condition was probably present. The two patients who recovered had fractures of the pelvis and one had also a compound fracture of the tibia and fibula with gas bacillus infection. The two additional patients who died had severe associated injuries and multiple fractures.

The mortality rate in this small number of cases is 60 per cent. This rate cannot be compared with some other recent figures found in the literature because there all types of injuries of the bladder are recorded and our cases were only those of severe nonpenetrating trauma, four out of the five patients having fractures. Peacock,[1] in 1939, reported a mortality rate of 14.4 per cent for rupture of the bladder but he reported only those cases complicating fracture of the pelvis. Culver and Baker,[2] in 1940, reported only 6.25 per cent mortality but they included all types of rupture of perforation; their only death was of a man injured during catheterization.

ASSOCIATED INJURIES AND COMPLICATIONS

BLADDER

1 L with fracture of pelvis
1 L with fracture of pelvis, compound fracture of tibia and fibula, and gas bacillus infection of leg
1 D with fracture of femur, tibia and fibula, rupture of kidney, and cerebral concussion
1 D with fracture of ribs, clavicle, humerus, and sternum
1 D with peritonitis

Intestine.—Rupture of the intestine occurred in thirteen cases, or 17 per cent, of this series of seventy-four. The mortality rate was 69 per cent.

Perforation of duodenum	2	Died	2
Perforation of jejunum	4	Died	3
Perforation of ileum	6	Died	4
Perforation of colon	1	Died	0
Total	13		9

One interesting case was that of a patient 42 years old, who was carrying a tub of ground meat in front of him and ran into a butcher's chopping block. Operation four hours later revealed a perforation of the sigmoid colon. The rent was closed with silk sutures and the patient recovered.

One patient, a man of 25 years, was crushed between two trucks. Operation was performed within one hour but no intra-abdominal pathology was found. The patient died within twenty-four hours and examination revealed a rupture of the third part of the duodenum with extensive retroperitoneal infiltration which had ruptured into the general peritoneal cavity.

The second case of rupture of the duodenum was in a 22-year-old boy who drove his motorcycle into a car. He had fractures of the fourth and fifth cervical vertebrae with paralysis, and died in twenty-one hours. Examination showed a rupture of the third part of the duodenum with generalized peritonitis.

One patient was a man of 72 years who had had an indirect inguinal hernia for many years. At 1 A.M. he found his hernia irreducible and at 8 A.M. his family doctor attempted reduction. Severe abdominal pain ensued, operation was performed at 4 P.M., a generalized peritonitis was found, and death followed.

Another patient, a young man of 21 years, fell out of a truck at 9 A.M. Six hours later he was admitted to the hospital in a state of shock. Diagnosis of rupture of the liver was made, treatment of shock was instituted, and the patient died thirty-five hours after injury without benefit of surgery. Examination revealed a rupture of the jejunum, hemoperitoneum, and also laceration of the lung with hemothorax.

Still another patient was a man of 62 years, who was struck in the abdomen by a pole of an auto trailer at 2 P.M. Nine hours later he was admitted and operated upon at once. A perforation of the ileum one foot proximal to the ileocecal valve was closed and then bilateral direct hernias were repaired. The abdomen was drained by means of two wicks, two tubes, and one piece of vioform gauze. The patient died thirty-nine hours after being injured with generalized peritonitis.

Poer and Woliver,[3] in 1942, reviewed and reported on 1,476 cases of rupture of the intestine and mesentery with a total mortality of 72.1 per cent. Operation was performed on 1,014 patients, of whom 603 died, an operative mortality of 59.5 per cent. But 462 patients died without operative intervention.

INTESTINE

13 cases

1 L with perforation of jejunum, pelvic abscess drained on ninth day
1 L with perforation of ileum
1 L with perforation of ileum, bronchopneumonia, and hydrothorax
1 L with perforation of sigmoid
1 D with perforation of duodenum
1 D with perforation of duodenum, fracture of the fourth and fifth cervical vertebrae
1 D with perforation of jejunum and hemothorax
1 D with perforation of jejunum
1 D with perforation of jejunum and fracture of tibia and fibula
2 D with perforation of ileum
1 D with perforation of ileum, strangulated hernia
1 D with perforation of ileum, bilateral direct hernias repaired

Kidney.—Of twenty-nine patients with injuries of the kidney, eighteen showed only hematuria and were discharged after an uneventful hospitalization. One patient required nephrectomy seventeen days after injury and the only other patient operated on underwent nephrectomy three years after injury. The three patients who died had serious associated injuries with multiple fractures.

Injuries of the kidney represent 39 per cent of this series. Three died, giving a mortality of 10 per cent.

Prather,[4] in 1940, reported twenty patients with injury of the kidney. Ten were listed as contussions with no deaths. One was listed as subcapsular rupture but did not die. Of the nine patients with lacerations, four died, giving a total mortality of 20 per cent. Lewis and Trimble,[5] in 1933, reported thirty cases of injury of the kidney. Twenty-one showed only hematuria. There were three deaths in their series, giving a mortality of 10 per cent.

KIDNEY

29 cases

18 showed only hematuria, rapidly improved
1 L with fracture of ribs and second and third lumbar vertebrae
2 L with fracture of pelvis
1 L with fracture of ribs
1 L with fracture of ribs, concussion of brain
1 L with fracture of ribs, radius, and ulna, and concussion of brain
1 L with concussion of brain
1 L with fracture of femur
1 D with fracture of ribs, tibia, and fibula, and fat embolism
1 D with fracture of ribs, clavicle, and hemothorax
1 D with fracture of skull, tibia, and fibula

Liver.—Sixteen patients, or 21 per cent of this series, had a diagnosis of rupture of the liver. Twelve died, giving a mortality rate of 75 per cent.

Operation was performed on only two patients. One was operated upon within twenty-four hours and died. The other was operated upon two months after being kicked by a horse, and a liver abscess and subdiaphragmatic abscess were drained; the patient recovered.

Three patients died within one hour after admission and four others died within twenty-four hours, so that 58 per cent of the deaths oc-

curred during the first hospital day. All of these patients had serious associated injuries with multiple fractures.

Lewis and Trimble[5] reported, in 1933, twenty cases of rupture of the liver. Fourteen of the patients were operated on, of whom six died, giving an operative mortality of 40 per cent. Four patients not operated upon died, so that the total mortality was 50 per cent.

LIVER

16 cases

2 L with no complications
1 L with subdiaphragmatic abscess
1 L with fracture of ribs and hemothorax
1 D with no complications
1 D with fracture of ribs
1 D with fracture of ribs and femur
1 D with fracture of ribs, mandible, and skull
1 D with fracture of ribs, rupture of spleen
1 D with fracture of ribs, hemothorax, and subdural hemorrhage
2 D with fracture of ribs and skull
1 D with fracture of ribs and hemothorax
1 D with fracture of pelvis, radius, and ulna, contusion of kidney, gas bacillus infection of arm, and fat embolism of lungs
1 D with fracture of ribs, pelvis, and humerus
1 D with fracture of ribs and femurs

Mesentery.—There was apparently only one case of rupture or tear of the mesentery without injury to other organs. The patient was in the psychiatric ward where he either fell or threw himself against the foot of the bed. Laparotomy revealed about 350 c.c. of blood in the peritoneal cavity and a rupture of the mesentery of the ileum. The patient recovered from the injury.

Pancreas.—A boy, aged 2 years, was hit by a truck, on the left side of the abdomen. Five hours later he was admitted to the hospital because of shock, pain in the left side of the abdomen and left side of the chest, and vomiting. An x-ray of the chest was negative. Two hours after admission laparotomy was performed and a rupture of the spleen was packed with one piece of viaform gauze. The patient died eighteen hours after operation and examination showed, in addition to the ruptured spleen, a laceration of the tail of the pancreas. This case is included with the injuries of the spleen.

Spleen.—There were nine patients with rupture of the spleen in this series, or 12 per cent. Five patients died, giving a mortality rate of 55 per cent.

All four patients who recovered underwent a splenectomy, even though one patient also had a fractured skull. It is interesting that the last four patients admitted to the hospital were the only ones recovering from this injury in the past fifteen years. There has been no death from rupture of the spleen since 1934. One patient died following a packing of the splenic tear. The other four patients that died had serious associated injuries and multiple fractures; three deaths occurred within the first twenty-four hours after admission.

One patient alone showed a latent bleeding time of five days. Harkins,[6] in 1942, reported that 48 per cent of cases had a latent period of two to six days and 28 per cent had a latent period of seven to eleven days. Maes and Rives,[7] in 1941, reported twenty-six cases with nine deaths, or 35 per cent mortality. Berger[8] reported, in 1902, that in 220 cases in which operation was not performed the mortality was 92.3 per cent.

Wright and Prigot,[9] in 1939, reported that among 20,000 patients admitted to their traumatic service, there were thirty cases of subcutaneous rupture of the spleen, or 0.15 per cent; among their patients with subcutaneous abdominal injuries, 48 per cent had rupture of the spleen. Mazel,[10] in 1932, reported an incidence of 30 per cent ruptures of the spleen with the same injuries.

SPLEEN

3 L with splenectomy
1 L with splenectomy and fracture of skull
1 D with fracture of ribs, tibia, and fibula, and laceration of kidney
1 D with "tear in spleen packed"
1 D with fracture of ribs, rupture of diaphragm, and hemothorax
1 D with fracture of ribs, second cervical vertebra, and femur
1 D with fracture of ribs and pelvis

Stomach.—One patient with rupture of the stomach is in this series. He was a youth of 18 years who was riding a motorcycle at night, ran into a car and received a blow by the handle bar. He was admitted to the hospital and operated upon at once. There was found a rupture of the left rectus muscle and a rupture of both the anterior and posterior walls of the stomach. Operation required two hours. Death occurred twenty-four hours after operation, from generalized peritonitis.

DISCUSSION

The differences in rates of incidence and mortality which are found in the literature are due possibly to the small number of cases of nonpenetrating abdominal trauma which any one writer is able to report. It must be noted that some reports cover operative mortality while others cover total mortality. Under these conditions a comparison of statistics is meaningless.

Estes,[11] in 1942, stated that of 2,217 injured patients admitted, thirty-two or 1.4 per cent were nonpenetrating abdominal trauma. Cody,[12] in 1939, wrote that of 5,744 accidents in Iowa, fifty-three or 0.9 per cent were of this type. Our statistics are not of the same type and therefore cannot be used for comparison.

Table VI shows the mortality rate by five-year periods. There has been a marked drop in the rate in the past five years. This improvement is due partly to the prompt operation on the last four patients with rupture of the spleen and recovery of all of them. In the last three years, of eighteen patients, five have received some type of sulfa drug. Of these eighteen, only three died. The drug probably had

some value in decreasing the mortality rate, but the number of cases is too small to be broken down into different types of injury. Certainly chemotherapy, especially the direct implantation of the sulfa drug into the peritoneal cavity in patients with perforation of the intestine, is strongly recommended.

TABLE VI

MORTALITY RATE BY FIVE-YEAR PERIODS

PERIOD	NO. PATIENTS	NO. DIED	RATE (PER CENT)
1927-1931	14	7	50
1932-1936	35	22	63
1937-1941	25	4	16

CONCLUSIONS

1. Seventy-four cases of nonpenetrating abdominal trauma are reviewed.

2. The incidence of these cases is small but the mortality is very high.

3. Mortality should be lessened by (a) proper training of first-aid workers, internes in accident rooms and wards and doctors; (b) use of plasma in shock; (c) operation within six hours if indicated; (d) proper use of the sulfa drugs intraperitoneally.

REFERENCES

1. Peacock, A. H.: Rupture of the Bladder, J. Urol. **42**: 1204-1206, 1939.
2. Culver, H., and Baker, W. J.: Rupture of the Urinary Bladder, J. Urol. **43**: 511-531, 1940.
3. Poer, D. H., and Woliver, E.: Intestinal and Mesenteric Injury Due to Nonpenetrating Abdominal Trauma, J. A. M. A. **118**: 11-15, 1942.
4. Prather, G. C.: Traumatic Conditions of the Kidney; Clinical Observations, J. A. M. A. **114**: 207-210, 1940.
5. Lewis, D., and Trimble, I. R.: Subcutaneous Injuries of the Abdomen, Ann. Surg. **98**: 685-692, 1933.
6. Harkins, H. N.: Delayed Splenic Rupture; Report of a Case, Am. J. Surg. **57**: 159-161, 1942.
7. Maes, U., and Rives, J. D.: Surgery of the Spleen, in F. W. Bancroft: Operative Surgery, New York, 1941, D. Appleton-Century Company, Inc., section XIX, p. 1,012.
8. Berger, E.: Die Verletzungen der Milz und ihre chirurgische Behandlung, Arch. f. klin. Chir. **68**: 865-914, 1902.
9. Wright, L. T., and Prigot, A.: Traumatic Subcutaneous Rupture of the Normal Spleen, Arch. Surg. **39**: 551-576, 1939.
10. Mazel, M. S.: Traumatic Rupture of the Spleen, Illinois M. J. **62**: 170-173, 1932.
11. Estes, W. L., Jr.: Non-penetrating Trauma of the Abdomen, South. Surgeon **10**: 427-440, 1941. Also: Surg., Gynec. & Obst. **74**: 419-424, 1942.
12. Cody, W. E.: Treatment of Traumatic Injuries of Abdominal Cavity, Its Wall and Contents, J. Iowa M. Soc. **29**: 549-555, 1939. Quoted by Estes, W. L., Jr. Loc.[11]

THE THERAPY OF SHOCK IN EXPERIMENTAL ANIMALS WITH SERUM PROTEIN SOLUTIONS

II. Fate in the Body of Concentrated and Dilute Serum and Saline Solutions

E. E. Muirhead, M.D., C. T. Ashworth, M.D., L. A. Kregel, M.D., and J. M. Hill, M.D., Dallas, Texas

(From the William Buchanan Blood, Plasma and Serum Center of Baylor University Hospital, Dallas)

A SEVERE freeze of one hind limb of a dog leads to a marked decrease in the plasma volume following thawing and fatal shock after six to eleven hours.[1] The animals expire after a variable interval of hypotension. In the present study the fate in the body of intravenously administered concentrated serum, dilute or half-strength serum, and 5 per cent glucose in physiologic saline solution in this type of shock was observed. No attempt at survival was made and the damaged limb was left intact.

VOLUMES OF SOLUTIONS USED

The average protein concentration for dilute serum was 3.8 Gm. per cent and for concentrated serum 15.8 Gm. per cent. In comparing the fate of these two solutions two criteria were observed, namely, (a) the volume of solution administered and the expected plasma volume increment in the body, and (b) the total grams of protein (albumin plus globulin) given in the entire infusion. Accordingly, two different volumes of each solution were selected (Table I, Part A).

Part B of Table I contains the average plasma volume and total circulating protein deficit for the corresponding groups during shock at the time the solutions were given.

METHODS

Mongrel dogs on meat and dog biscuit rations were used. Food was withheld for twelve to twenty hours prior to the experiment. The animals were subjected to pentobarbital sodium anesthesia approximately one hour before the freeze.

The procedure for producing the freezing injury and the methods used in studying the changes in shock and following therapy have been described.[1]

The plasma concentrations of T-1824 dye and thiocyanate were made with the aid of a dual-cell photoelectric colorimeter. A stable hemoglobinemia developed and corrections for hemoglobin staining of

Received for publication, March 5, 1943.

TABLE I

SOLUTION		PART A* AVG. VOL. (C.C.)	PART A* AVG. PROTEIN CONTENT (GM.)	PART B† AVG. DECREASE IN PLASMA VOL. IN SHOCK (C.C.)	PART B† AVG. DECREASE IN CIRC. PROTEIN IN SHOCK (GM.)
5% glucose in saline		300	none	279	17.58
Dil. serum	(1)	325	11.5	428.7	26.5
	(2)	595	25.6	427	29.9
Conc. serum	(1)	86.2	12.5	348	21.2
	(2)	107	18.2	288	17.4

*The average volume and grams of proteins for each type of solution used are given.

†The average decrease in plasma volume (cubic centimeters) and decrease in total circulating proteins (grams) for each group are given.

plasma were not made for the dye method. Following therapy, methemoglobinemia was present in several experiments.

One hour was allowed for thiocyanate equilibration. The thiocyanate levels varied from 3 to 11 mg. per cent.

Hemoglobin and plasma protein concentrations were determined on venous blood periodically after therapy until death ensued. The samples of blood were obtained from exposed femoral and jugular veins and purified heparin was used as anticoagulant.

At the time the hypotension (50 to 80 mm. Hg) developed the peripheral veins and arteries were contracted, and the blood was thick and dark. The intravenous solutions were given at this time.

Serum and dialysed plasma were used because previously we[2] had noted that concentrated plasma prepared from citrated blood contained a sufficient concentration of sodium citrate to precipitate tetany in dogs when rapid injections of 25 to 50 c.c. were made. This transient calcium binding effect, if sufficiently severe, may be fatal to dogs in shock. It thus became apparent that conclusions of shock therapy with concentrated citrated plasma in animals were subject to doubt unless rates and volume of injections comparable to those observed in human beings on body weight basis be observed.

Eleven animals received serum obtained by defibrination and desiccation by the adtevac process.[3] Three animals received plasma after the citrate was dialysed out. All preparations were tested for toxicity by injecting 25 to 50 c.c. of the concentrate intravenously into normal dogs. No toxic effects were observed.

The concentrated serum was injected into the femoral vein (normal side) by means of 50 c.c. syringes. The rate of injection averaged 3.1 c.c. per minute (0.35 c.c. per minute per kilogram weight) when the entire time elapsing for the administration is considered. It is emphasized, however, that the injections were given intermittently, usually 5 to 10 c.c. in one minute or less followed by an interval of three to five minutes for physiologic accommodation. This procedure seemed

reasonable since in the human being we usually give 50 to 150 c.c. in two to ten minutes and wait fifteen to thirty minutes before the next dose.

Dilute serum and saline solutions were given continuously by drip system. The average rates of administration were 10.5 c.c. per minute (1 c.c. per minute per kilogram weight) for dilute serum and 11.5 c.c. per minute (1.2 c.c. per minute per kilogram weight) for glucose-saline solution.

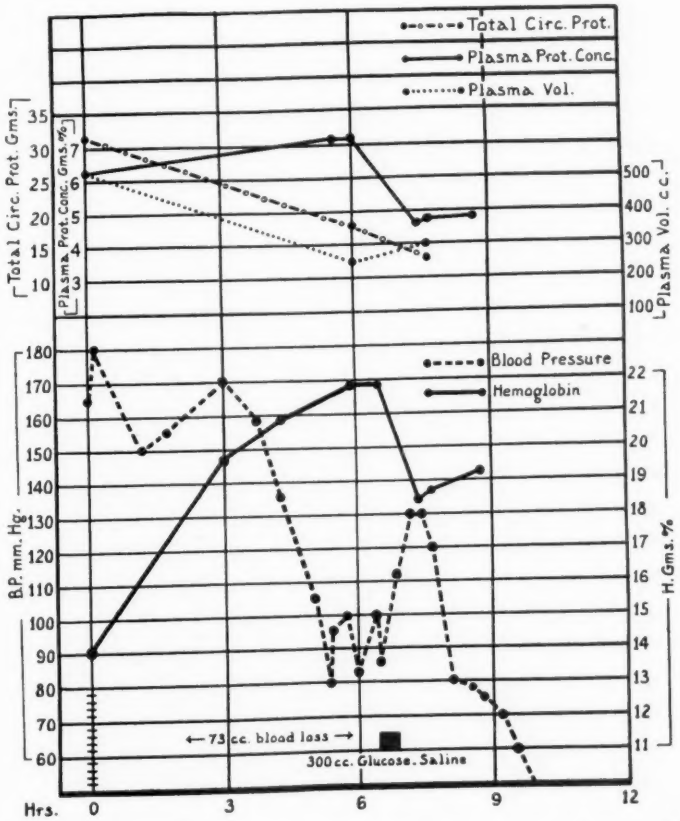


Fig. 1.—This figure represents a typical example in the glucose-saline group. Notice that the venous hemoconcentration was elevated to 21.9 Gm. per cent in shock from a control level of 14 Gm. per cent. Shortly after the infusion a dilution to 18.3 Gm. per cent occurred but a hemoconcentration to 19.15 Gm. per cent reappeared 1.5 hours later. At the same time the plasma protein concentration dropped from 7.1 Gm. per cent during shock to 4.6 after therapy and persisted at this level. (Dog weight 9.8 kg.)

RESULTS

I. Effects on Hemodilution and Plasma Volume.—A. *Saline Solution:* This solution produced a dilution of red cells and circulating plasma proteins. The venous hemodilution was not complete or persistent and by the time the animals died a hemoconcentration approaching that of the shock level reappeared, but, at the same time, the dilution of the plasma proteins remained pronounced (see Table II).

TABLE II

REMARKS	INTERVALS	MEAN ARTERIAL PRESSURE MM./HG	HEMOGLOBIN (GM.)	HEMATOCRIT (%)	R.B.C. (MIL.)	PL. VOL. (C.C.)	PL. VOL. DECREASE (% OF CONTROL)	PL. VOL. DECREASE (% OF BODY WT.)	PL. PROT. CONC. (GM. %)	T. C. P. (GM.)	CHANGE T. C. P. (GM.)
Average figures	Control	156.0	13.43	43.3	6.12	535.2			6.17	35.95	
5 dogs, wt. 8.52 kg.	7.4 to 7.9 hr. shock	62.0	20.7	72.7	9.63	256.0	−51.14		6.09	18.61	−17.58
glucose-saline group	12 min. after R	88.4	15.5	47.2	7.05						
blood loss 85 c.c.	33 min. after R	99.0	16.85			303.2		−3.26	3.73	12.46	− 6.15
died 2 hr.	1.75 hr. after R	63.2	18.44						4.73		
Average figures	Control	142.0	13.05	38.2	6.23	855.0			6.65	55.9	
3 dogs, wt. 11.4 kg.	8.1 to 9 hr. shock	61.0	18.9	64.2	9.9	426.3	−51.0	−3.76	6.55	27.76	−26.5
325 c.c. dil. ser. with	0.83 hr. after R	112.0	14.2	44.8		630.1			5.55	34.8	+ 7.06
11.5 Gm. prot. blood	2.9 hr. after R	57.6	15.9	48.5					5.88		
loss 58 c.c.											
Average figures	Control	142.5	13.1	39.7		735.0			6.75	49.6	
2 dogs, wt. 9.1 kg.	10.5 to 11.25 hr. shock	55.0	19.25	68.0		308.0	−57.85	−4.8	6.68	20.7	−29.2
595 c.c. dil. ser. with	0.94 hr. after R	112.5	11.95						5.7	37.3	+16.6
25.6 Gm. prot. blood	2.5 hr. after R	123.0	13.55						6.48		
loss 48 c.c.											
Average figures	Control	162.5	13.2	40.2	6.33	646.0			6.0	38.7	
4 dogs, wt. 9.85 kg.	5.45 hr. shock	65.2	18.94	62.5	9.68	298.0	−53.5	−3.53	5.84	17.47	−21.2
conc. prot.	27.5 min. after R	120.7	15.3	47.0	7.0	476.0			6.71	30.4	+14.36
Solutions 86.2 c.c.	1.2 hr. after R	129.5							6.39		
with 12.5 Gm., prot.	4.12 hr. after R	76.5	15.1								
blood loss 68 c.c.											
Average figures	Control	141.0	13.3	41.6	6.11	583.0			6.2	36.7	
5 dogs, wt. 9.08 kg.	6.0 hr.	96.8	19.3								
conc. serum 107 c.c.	8.15 hr. shock	57.8	18.9	64.4	9.7	295.0	−49.1	−3.17	6.5	19.3	−17.4
with 18.2 Gm. protein	34.8 min. after R	103.8	13.8	41.1	6.18	624.4			6.9	43.0	+23.8
blood loss 84.4 c.c.	1.24 hr. after R	103.8	12.76								
	5.75 hr. after R	84.0	16.4								

The figures given are average figures for each group. The blood loss was the loss sustained through the blood samples for the various determinations. Average figures are given because the individual experiments were observed to display the same trend.

Abbreviations: Pl. Vol., plasma volume; Pl. Prot. Conc., circulating plasma protein concentration; T. C. Prot., total circulating plasma proteins; change in T. C. P., the decrease in total circulating proteins in shock and the change after therapy; R, therapy (infusion); hr., hours.

For this group the average plasma volume decrease in shock was 279 c.c. (51.1 per cent of control level). Thus the 300 c.c. infusion was greater than the determined deficit. Plasma volume determinations 33 minutes after the infusions revealed an average volume of 303.2 c.c. (47.3 c.c. greater than shock level) indicating that within one-half hour as much as 84.2 per cent of the infused solution escaped from the circulation.

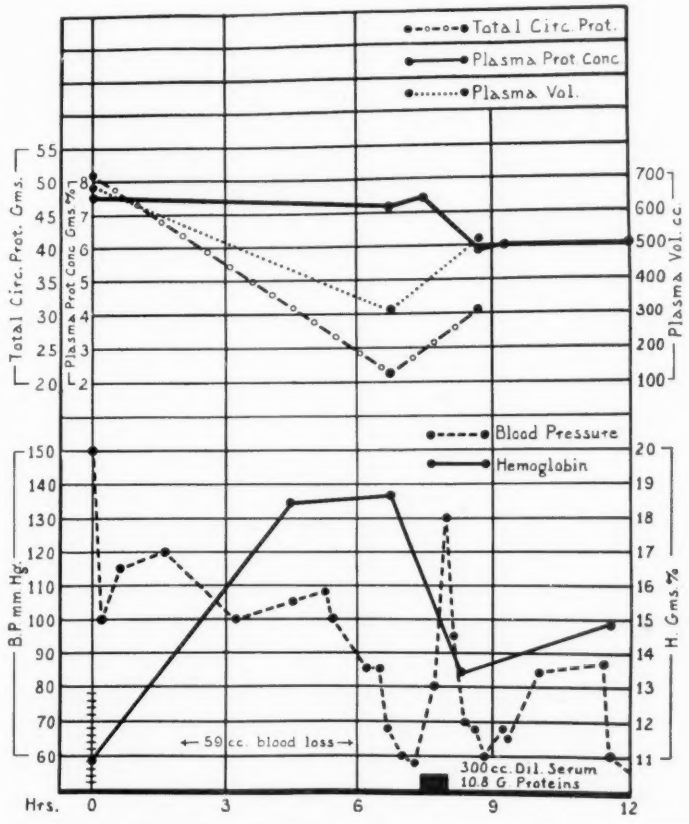


Fig. 2.—A typical example receiving a smaller volume (300 c.c.) dilute serum. The hemoglobin concentration was increased from a control level of 10.95 Gm. per cent to 18.65 in shock. Within thirty minutes after the infusion it had dropped to 13.4 Gm. per cent but at 3.6 hours after the infusion it was 14.9. Thus there was an increase of 7.7 Gm. per cent in shock with an ultimate decrease of 3.75 Gm. after the infusion. The plasma protein concentration was lowered from 7.1 Gm. per cent in shock to 5.9 Gm. per cent thirty minutes after the infusion and remained at this level (6 Gm. per cent) 3.6 hours later. (Dog weight 10 kg.)

B. *Dilute Serum:* This solution is actually composed of one-half volume of normal serum and one-half volume of saline solution.

The smaller volume of dilute serum (avg. 325 c.c.) produced a hemodilution more marked thirty minutes after the infusion than at any subsequent period. About two hours the hemoglobin concentration reached a temporary stable level, which was approximately halfway between the control and the shock levels. At the same time the red cells were diluted there was a persistent dilution of the circulating

plasma proteins, a dilution half as pronounced as following saline solution alone. The hemodilution occurred in conjunction with an increase in the plasma volume, but 0.83 hour after the infusion the average plasma volume increment accounted only for 62.7 per cent of the volume infused. Thus, at this time 37.3 per cent of the infused solution had escaped the circulation and in view of subsequent hemoconcentration it is safe to state that eventually at least 50 per cent of the infused volume left the circulation.

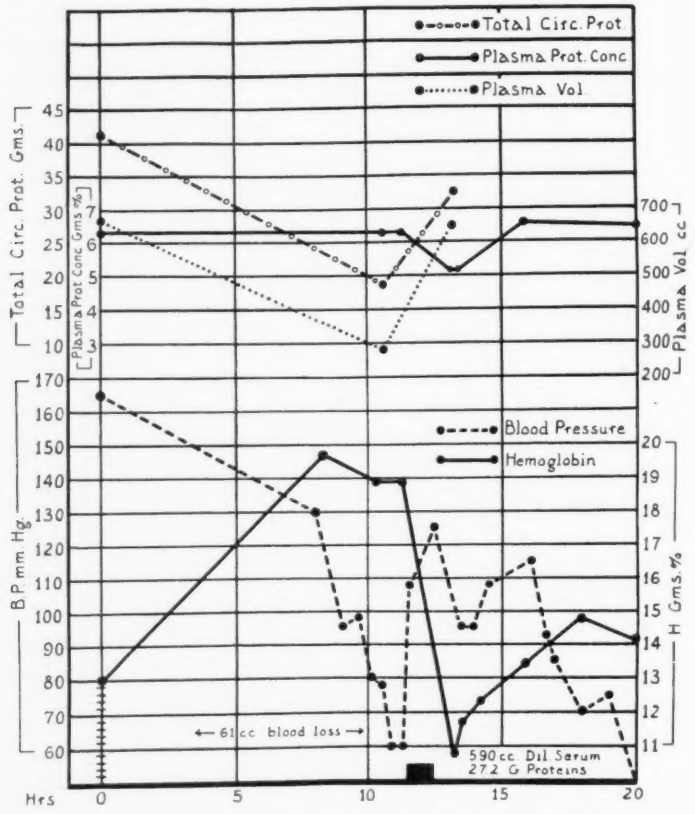


Fig. 3.—Example of large volume dose (590 c. c.) of dilute serum group. Notice the reappearing hemoconcentration and an increase in plasma volume much less than expected from the volume infused. The transient decrease in plasma protein concentration is depicted in the troughlike curve. (Dog weight 10 kg.)

The initial hemodilution following the larger volume of dilute serum (avg. 595 c.c.) was, as expected, twice the magnitude of that following the lesser volume of similar solution. Again the hemoglobin level progressively increased indicating an escape of fluid from the circulation. According to the plasma volume studies at an average of 0.94 hour after the infusions the plasma volume increment accounted for only 56.9 per cent of the volume infused. The plasma protein concentration of the recipient was lowered for three hours during and after the infusions indicating further the entrance and loss of fluid from the circulation.

C. *Concentrated Serum:* This solution contains not only concentrated proteins but also concentrated salts of serum, mainly sodium chloride. Upon its injection intravenously there followed a prompt hemodilution, i.e., a decrease in hemoglobin concentration, red cell count, and hematocrit.

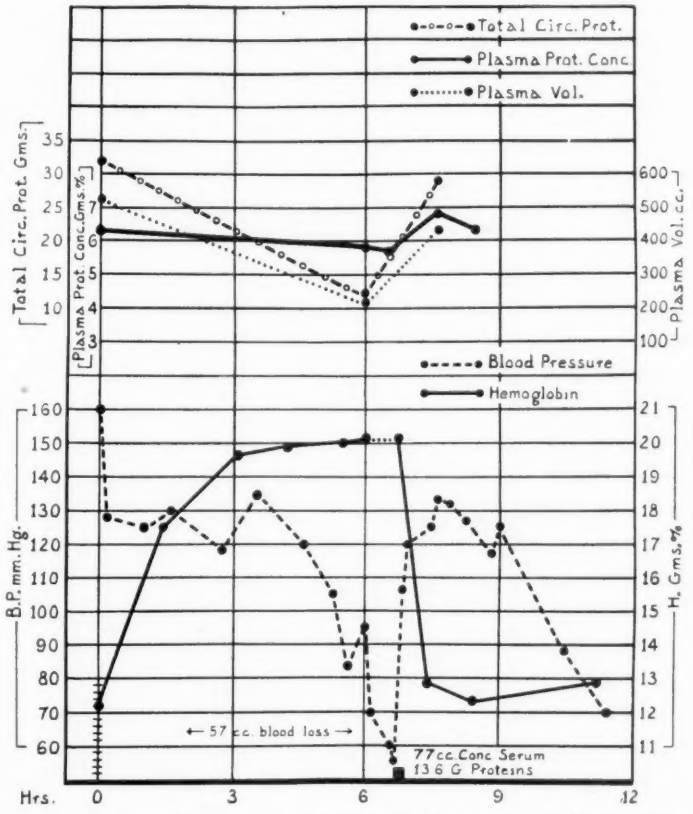


Fig. 4.—Example of smaller dose of concentrated serum effecting near complete replacement of plasma volume (compare with Fig. 5). The prompt hemodilution and increase in plasma volume with slight elevation of plasma protein concentration are demonstrated. (Dog weight 9.1 kg.)

The estimation of the circulating plasma volume in shock on the basis of the changes in venous hemoglobin concentration, red blood cell count, or hematocrit is grossly inaccurate as a result of the sequestration of red blood cells in the capillaries and venules during shock (vide infra). The venous hemodilution following concentrated serum was greater than expected from the volume of fluid injected but not always as great as expected from the amount of protein given. This discrepancy seemed to result from the release of sequestrated red cells from the capillary regions to the general circulation; particularly noticeable on the venous side (vide infra). When one examines the plasma volume studies, however, it becomes apparent that the plasma volume increment following the concentrate far

exceeded the amount of fluid injected. In the examples graphed (Figs. 4, 5, and 6) the plasma volume increment amounted to 3 to 3.5 times the volume of fluid injected as expected in view of the degree of concentration of approximately 3 to 3.5 times normal.

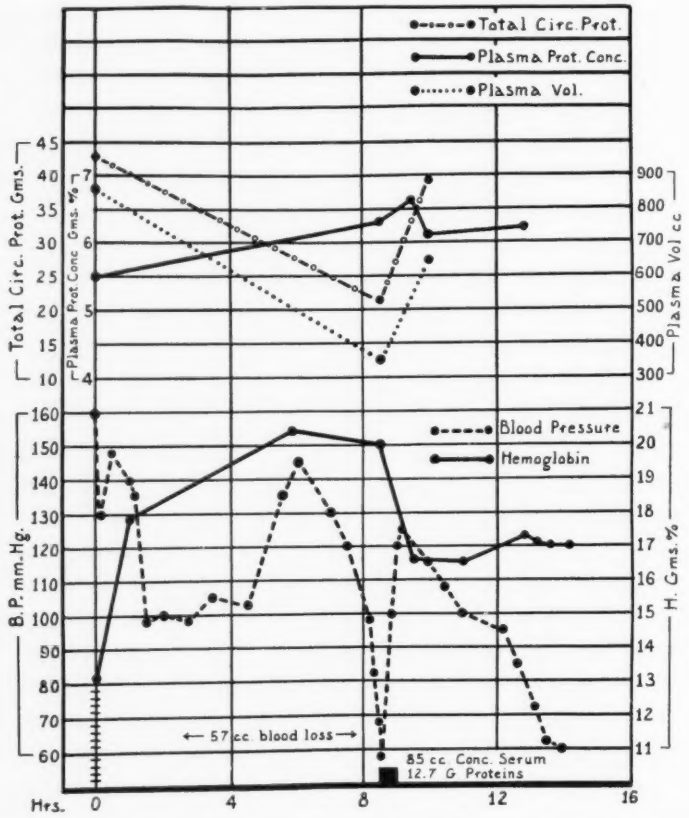


Fig. 5.—Example of smaller dose of concentrated serum. The trend of events is similar to that in Fig. 4, but failure of complete replacement of plasma volume is demonstrated. (Dog weight 10 kg.)

Animals of fairly similar body weights and having the same degree of hemoconcentration (elevation of venous hemoglobin) may display different degrees of hemodilution following similar doses of concentrated serum (Figs. 4 and 5). The demonstrated explanation for this discrepancy is that certain animals normally have larger plasma and red blood cell volumes than others despite the similarity in body weights. For reasons not completely understood, a severe freeze of hind limb gives rise to a fairly constant plasma volume decrement on a percentage basis (50 to 60 per cent). Thus, similar doses of concentrated serum may constitute adequate plasma replacement (Fig. 4) or may fail by 40 per cent in replacement in other animals (Fig. 5) despite similar hemoglobin concentrations before and during shock in such cases. In each of these cases, however, the actual plasma volume increment was as expected from the amount of protein given (vide infra).

Discussion of Plasma Volume Changes.—The Starling-Landis[4, 5] concept of capillary fluid exchange offers a means of analyzing the observations made. With the onset of the severe hypotension of shock a substantial drop in capillary pressure must occur for several reasons: venous hemoconcentration becomes stabilized, the head pressure maintaining the capillary pressure is critically lowered, the capillaries are generally dilated and packed with red cells (stasis).* Any elevation of the arterial pressure at this time must be partly transmitted to the capillaries, a change substantiated by the increase in size of the damaged limb following glucose-saline solution.

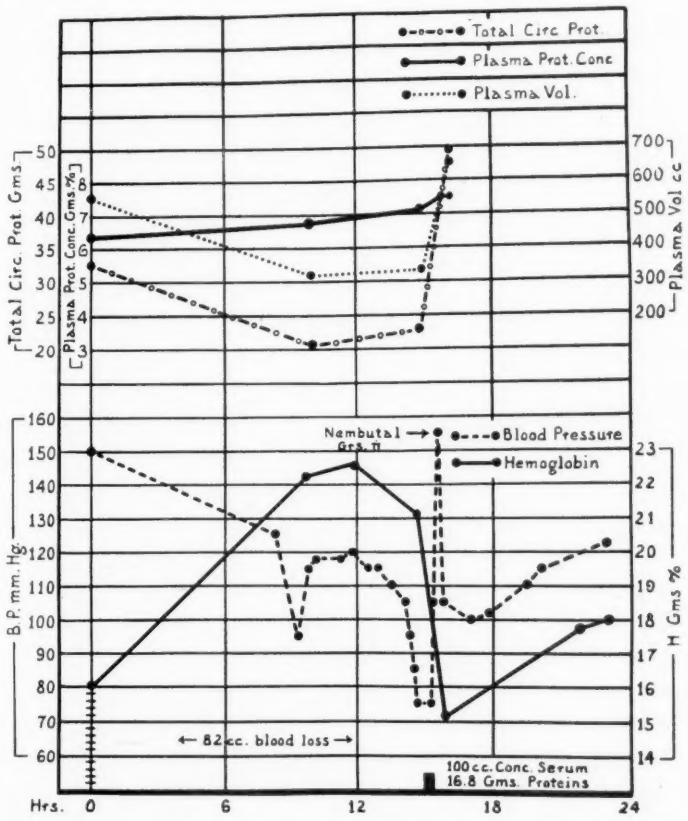


Fig. 6.—Example from large volume of concentrated serum group. The trend of changes are similar to those following a smaller volume but replacement is more complete. The depression of blood pressure following nembutal is demonstrated. (Dog weight 8.8 kg.)

Following an infusion of glucose-saline solution most, if not all, of the solution leaves the circulation in a short time. During this change the plasma protein concentration is lowered and the arterial pressure is transiently elevated. A situation seems to be created whereby the out-

*Landis[5] has described the series of events in the development of stasis. When the capillary is damaged it becomes permeable to whole plasma fluid and as the plasma escapes into the tissues, the red blood cells become packed at the venous end, producing a partial block. Plasma fluid loss is temporarily enhanced, red cell packing becomes more pronounced until the capillary is stuffed with erythrocytes. At this time the capillary pressure drops markedly.

going force in the capillaries appears to be increased but the fluid-withholding force (effective colloidal osmotic pressure) is lowered. Such changes must upset markedly the fluid-withholding factors which, together with the increased capillary permeability, precipitate a rapid passage of fluid into the tissues. There follows then a rapid reversion to the former state of circulatory insufficiency.

In a similar manner dilute serum appears to upset the fluid withholding forces but only about half of the solution is lost initially, apparently as a result of the fluid-withholding properties of the injected proteins.

The increase in plasma volume following concentrated serum is greater than the volume of fluid injected. The solution has a greater osmotic pressure than the ordinary body fluids. When given into a vein it must increase the effective plasma colloidal osmotic pressure which at the capillaries pulls fluids from the tissues into the blood stream. The shift of fluid swells the plasma volume and the plasma fluid plus red cells are conducted back to the heart via venules and veins.

The plasma protein concentration is normally well protected. The present observations indicate that fluid is lost from the circulation following the dilution of the proteins and fluid is added to the circulation following the concentration of the proteins. Theoretically, after a period of equilibration, the plasma volume increment following the injection of protein solutions, expressed as multiples of 100, should be equal to the ratio of the total grams of protein injected and the normal plasma protein concentration of the recipient. A formula may be stated for this purpose as follows:

$$\text{Plasma volume increment of recipient in c.c.} = \frac{\text{Total Gm. of protein injected}}{\text{Plasma protein concentration of recipient}} \times 100$$

The volume given by this formula is strictly a theoretic one and it may be termed the expected plasma volume increment. Under the conditions of the present experiments it is modified by the presence of capillary damage, a factor encouraging the loss of proteins from the circulation and affecting the ultimate soundness of these assumptions. The formula, therefore, will be used only for an analysis of the immediate effects of the solution.

In Table III a comparison is made between the theoretic expected volume increment by the various solutions on an injection protein basis and the actual volume increment as determined by the dye method. The two volumes, expected and actual, compare favorably and demonstrate grossly that the volume increment by the solutions is dependent on the amount of protein injected.

II. Effects on the Sequestration of Red Blood Cells in Capillaries and Venules.—Cannon,[6] as a result of studies during World War I, pointed out that the red cell count, hemoglobin concentration, and

TABLE III

A Comparison of the Theoretical Expected Volume Increment in the Recipient on the Basis of the Total Grams of Protein Given and the Actual Volume Increment as Measured by the Dye Method

SOLUTION	VOLUME (C.C.)	PROTEIN CONTENT (GM.)	THEORETICAL EXPECTED VOLUME INCREMENT		ACTUAL VOLUME INCREMENT DYE METHOD		
			VOLUME (C.C.)	% OF VOLUME GIVEN	VOLUME (C.C.)	% OF VOLUME GIVEN	INTERVAL AFTER INJECTION (MIN.)
Glucose-saline	300	0	0	0	47	15.6	33
Dilute serum	325	11.5	173	53.2	204	62.7	50
Dilute serum	595	25.6	379	63.8	337	56.6	56
Conc. serum	86.2	12.5	173	200.0	178	206.4	27
Conc. serum	107	18.2	294	274.8	329	307.4	35

hematocrit of capillary blood were much higher than similar simultaneous studies on venous blood in cases of wound (traumatic) shock. This change in red cell-plasma ratio has been interpreted as resulting from a sequestration of red cells in capillaries.

The plasma volume changes in our experiments as obtained by the degree of venous hemoconcentration in shock and venous hemodilution following therapy* were compared with the plasma volumes as determined by the dye technique.

It was observed that in each instance (eighteen dogs) the plasma volume in shock as obtained by the dye method was substantially lower than the volume obtained by the hemoglobin factor and the venous hemoconcentration. This discrepancy is taken to indicate that the venous hemoconcentration, although pronounced, did not reflect the degree of plasma fluid loss within reasonable limits. The failure of venous hemoconcentration to reflect the degree of plasma deficit attains greater significance when it is considered that actually a greater number of red cells were present in the general circulatory system after the freeze since the spleen was firmly contracted at this time, a change which tends to produce results converse to those obtained. These findings are demonstrated in Table IV.

The only logical explanation for the above findings is that red cells become trapped in the capillaries in great numbers, as Cannon pointed out, and that this removal of red cells from the venous circulation accounts for the failure of the venous hemoconcentration to account for all of the plasma deficit. Microscopic examination of various tissues support this contention.[1] Let us examine the relation of the sequestration of erythrocytes in capillaries and therapy with saline, dilute serum, and concentrated serum solutions.

*The procedure used was as follows. The product of the control plasma volume and the venous hemoglobin concentration prior to anesthesia yielded a factor (hemoglobin factor). Subsequent changes in plasma volume, expressed as multiples of 100, were obtained by the ratio of this factor and subsequent venous hemoglobin concentrations. The loss of blood through samples collected was fairly even in the various experiments and comparison of results between groups seemed grossly unmodified by this one variant.

TABLE IV

EXPERIMENT	REMARKS	HB. (GM. %)	HB. FACTOR	PLASMA VOL. DYE (C.C.)	PLASMA VOL. HB. (C.C.)	PLASMA VOL., INCREMENT DYE METHOD (C.C.)	PLASMA VOL., INCREMENT HB. METHOD (C.C.)	HEMATOCRIT (%)	WHOLE BLOOD (VOL. C.C.)	R.B.C. (VOL. C.C.)
300 c.c. glucose saline solution. Blood loss, 73 c.c.	Control	14.0	72.3	517				43.1	909	392
	6 to 6.5 hr. shock	21.9		250	330			77.0	1087	837
	16 min. after R				395			63.1		
	33 min. after R	18.65		300	387	50	57	65.3	864	564
	1.5 hr. after R	19.15			376			6.76		
375 c.c. dil. serum with 14.1 Gm. prot. Blood loss, 62 c.c.	Control	12.65	130.3	1030				35.3	1592	563
	8.5 to 9 hr. shock	18.9		545	689			68.0	1703	1158
	1.5 hr. after R	14.15		810	920	265	231	52.0	1687	877
	2.75 hr. after R	15.4		846						
590 c.c. dil. serum, 27.2 Gm. prot. Blood loss, 61 c.c.	Control	13.0	85.8	660				40.4	1107	447
	11 to 11.5 hr. shock	18.9		291	454			68.0	909	618
	53 min. after R	10.8		645	793	354	339	33.6	971	326
	3.5 hr. after R	13.4			640			44.5		
	5.5 hr. after R	14.8			580					
85 c.c. conc. serum with 12.7 Gm. prot. Blood loss, 57 c.c.	Control	13.1	112.0	855				41.4	1459	604
	8.5 hr. shock	20.0		345	560			75.0	1380	1035
	30 min. after R	16.6			674			52.4		
	1 hr. after R			645		300	114		1372	727
	4 hr. after R	17.2			651			53.0		
	5 hr. after R	17.0			658					
100 c.c. conc. serum with 18 Gm. prot. Blood loss, 60 c.c.	Control	13.2	62.0	470				38.5	764	294
	6.5 to 6.8 hr. shock	19.5		272	318			60.0	680	408
	36 min. after R	14.4		600	430	328	112	43.0	1052	452
	1.1 hr. after R	14.4			430					
	3 hr. after R	15.5			400					
	5 hr. after R	15.0			413					

A comparison of the plasma volume as determined by the T-1824 dye method and the plasma volume as calculated from the degree of venous hemoconcentration in shock and venous hemodilution following therapy is given. The whole blood volume and red cell mass as determined by the plasma volume and venous hematocrit are also included. Notice the marked discrepancies in the latter.

Following therapy with glucose-saline and dilute serum solutions the plasma volume as estimated by the hemoglobin factor and the lowered venous hemoglobin concentration (venous hemodilution) continues to be far greater than the plasma volume as determined by the dye method. Yet, the plasma volume increment by each method was approximately the same, being slightly greater by the hemoglobin factor method in the saline group and slightly less in dilute serum group. These findings suggest that neither of these solutions appreciably alters the sequestration of red cells in capillaries. This concept is further supported by microscopic studies of the viscera following these solutions (vide infra). Capillareo-venous stasis, as gauged by the latter method, is not appreciably changed. By utilizing the averaged data given in the tables in a similar manner, it is observed that the above relationship between the dye method and the hemoglobin method of observing plasma volume changes holds true for all of the experiments in these two groups.

When the data for the concentrated serum groups are analyzed different results are obtained. In the several experiments in which dye volumes were determined and the degree of blood loss through samples was about even, only one revealed an appreciably greater volume by the hemoglobin method following therapy. In all instances the plasma volume increment following therapy was substantially lower by the hemoglobin method as compared to the dye technique. The usual finding (Table IV) revealed that the venous hemoglobin dilution accounted for less than one-half of the plasma volume increment. Further, microscopic examination of the tissues following concentrated serum demonstrated a decrease in the degree of capillareo-venous stasis.

The above findings suggest that concentrated serum produces a release of red cells from the capillaries into the general circulation.

Table IV also demonstrates that computation of the whole blood volume and total red blood cell mass by the venous hematocrit in this form of shock is grossly unreliable.

III. Effects on the Plasma Protein Concentration and Total Circulating Proteins.—In the present studies the plasma protein concentration was not consistently increased or decreased as shock development. On eight occasions the protein concentration was slightly increased, in seven instances it was slightly lowered, and three times it remained unchanged. In each case there was a considerable decrease in the total circulating proteins, a drop which in seventeen dogs averaged 50 per cent of the control level, indicating that the fluid lost from the circulation was whole plasma fluid. With this background in mind the effect of the three solutions on these two factors will be analyzed.

A. *Saline Solution:* The plasma protein concentration of the recipient was markedly lowered following this infusion of slightly greater volume than the plasma volume deficit. This was a persistent lowering

and remained after most of the saline fluid had escaped from the circulation.

These observations, similar to those of Beard and Blalock,[7] indicate that protein leaves the circulation following such infusions. This point was evident when the plasma volume studies were analyzed. By the latter method the decrease ranged from minus 3.95 Gm. to minus 12.5 Gm., an average of thirty-three minutes after the infusions were completed. By the average figures (Table II) it is observed that decrease amounted to an average of minus 6.15 Gm. below shock total protein level. The secondary decrease following the infusions produced an over-all decrease (shock exudation plus postinfusion loss) amounting to 66 per cent of the control level.

B. *Dilute Serum:* A smaller volume of this solution produces a persistent decrease in plasma protein concentration of the recipient, half as marked as that following glucose-saline infusions. The plasma volume studies indicated that the increase in total circulating proteins of the recipient was less than expected from the total number grams infused. An average of 11.5 Gm. of protein were infused but fifty minutes later there was an average increase of only 7.06 Gm. or 61.3 per cent of the amount given.

When the larger volume of dilute serum was given there was a decrease in protein concentration for 1.5 hours. An average of 25.6 Gm. of protein was infused but after fifty-six minutes the increase amounted to 16.6 Gm. or 60.9 per cent of the amount given.

C. *Concentrated Serum:* The plasma protein concentration was slightly increased, average of 0.5 Gm. per cent after 1.5 hours for both doses. According to the plasma volume studies, the total circulating proteins were increased to an extent slightly greater than the amount given.

Conclusion: Immediately following infusions of glucose-saline and dilute serum in shock further protein is lost from the circulation as the saline fractions pass to the tissues. By considering the volume of infusion lost according to the plasma volume studies and the amount of protein lost, it is calculated that the fluid escaping the circulation contained 2.4 Gm. per cent of protein for the glucose-saline group and 2.27 Gm. per cent for dilute serum.

IV. Effects on the Mean Arterial Pressure.—The mean arterial pressure following a severe freeze of one hind limb passes through certain fairly consistent stages. Immediately following the freeze there is usually a prominent drop which averaged 36 mm. Hg. Following the primary drop, there is a period of several hours during which the pressure is elevated toward the control level, following which severe hypotension ensues. If no therapy is instituted at this time, the animal dies either shortly thereafter or after a varying period of hypotension.

The solutions were administered in each case when the stage of severe hypotension ensued. The subsequent average arterial pressure changes are given in Table V.

None of the solutions produces a lasting elevation of the blood pressure. The glucose-saline solution was least effective and the sudden drop in pressure was closely associated with the just as sudden decrease in plasma volume. Next in line in the order of effectiveness were smaller volume of dilute serum, smaller volume of concentrated serum, larger volume of dilute serum, and larger volume of concentrated serum. In the last two groups the arterial pressure eventually declined despite an adequate circulating volume indicating that other complications were responsible for eventual death.

Arterial Pressure Changes Immediately Following Intravenous Concentrated Solutions: A rapid intravenous injection of certain volumes of concentrated serum was observed to produce a transient depression of the mean arterial pressure. When 5 to 10 c.c. of concentrated serum were injected in twenty seconds or less the arterial pressure dropped to 5 to 20 mm. Hg for an interval of 30 to 120 seconds. On each occasion the pressure came back to a level near or slightly above the preinjection level. This depressor effect gave rise to a steppage curve in which the ultimate effect was a substantial elevation of the pressure (see Fig. 7). In the entire concentrated serum groups there was an ultimate arterial pressure rise which averaged 57 mm. Hg above the average shock level.

The transient depressor effect was observed to vary according to the volume injected and the level of the arterial pressure. The animals appeared to be most sensitive in the region of 50 to 70 mm. Hg. A larger volume produced a more marked depression. Thus, in Fig. 7 it can be observed that the 10 c.c. doses produced a more prominent depression than the 5 c.c. doses. One animal (8 S) to which 35 c.c. of the concentrate were given when the arterial pressure reached the level of 20 mm. Hg showed a prompt elevation and the depressor effect became evident only when the pressure reached levels between 70 and 85 mm. Hg. At the time the injection was begun in this animal, terminal gasping respirations with side movements of the jaw were present. The latter ceased when the arterial pressure was elevated. Later on a second larger dose of 27 c.c. produced a prominent transient depressor effect.

These transient arterial pressure depressions following injection of concentrated serum by vein in animals in a severe state of oligemia do not correspond to the depressions termed speed shock by Herschfeld and Hyman, for several reasons. These investigators observed a transient arterial pressure drop following 1 to 5 c.c. intravenous injections of various solutions, yet we did not observe this effect following numerous rapid injections of Evans blue dye and thiocyanate solutions of 2 to 5 c.c. volumes. Moreover, the administration of glucose-saline and dilute serum at the rate of 10 c.c. per minute was not accompanied by such changes, but on the contrary, these solutions gave rise to a steady pressure increment. In addition, the ultimate effects of the

concentrated serum injections were in each case a substantially higher pressure than before the injection.

In a subsequent paper we will discuss further the transient depressor effect. The effect seems to depend on the rate of injection and the action of the concentrate in the heart-lung region. The effect can be completely eradicated by injecting the solution more slowly. Similar doses of normal solution have not initiated the depressor response in our hands. On a body weight basis the doses given per unit of time are grossly much greater than the usual doses given to patients clinically, which probably accounts for the fact that we have not observed this brief depressor effect clinically.

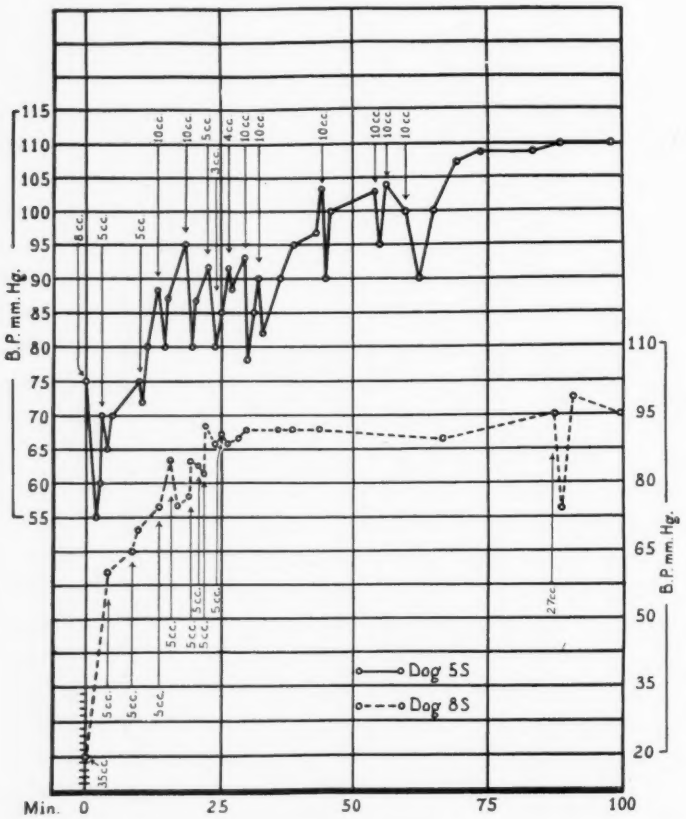


Fig. 7.—This figure represents the depressor effect resulting from the rapid administration of concentrated serum. Ordinarily the 10 c. c. doses were injected in ten seconds. Notice the difference between the effect at 50 to 75 mm. Hg and at 20 mm. Hg.

Fig. 6 demonstrates the effect of pentobarbital sodium on the arterial pressure following a successful elevation by concentrated serum. This procedure became necessary because of awakening by the animal on four occasions, but did not appear to mar the subsequent course completely.

V. Effects on the Fluid Available for the Solution of Thiocyanate and Plasma Sodium Concentration.—The fluid available for the solution

of thiocyanate has been considered to represent, for the most part, the extracellular fluid. Previously, it was pointed out[1] that without any evidence of an increased external loss of fluid, the fluid available for sodium thiocyanate solution is markedly reduced in freezing shock when the severe hypotension ensues. At the same time an elevation of the plasma sodium concentration, greater than expected from the degree of hemoglobinemia, was observed.

TABLE V

MEAN ARTERIAL (CAROTID) PRESSURE CHANGES*

REMARKS	5% GLUCOSE IN SALINE SOLUTION	DIL. SERUM SMALLER VOL.	CONC. SERUM SMALLER AMT.	DIL. SERUM LARGER VOL	CONC. SERUM LARGER AMT.
Number of dogs	5	3	3	2	5
Hr. before shock, avg.	7.9	8.8	6.5	11.2	8.2
Before freeze	156.0	142.6	161.0	147.5	141.0
Primary drop	164.0	109.6	122.6	112.5	104.2
Severe hypotension	64.0	61.0	60.7	55.0	57.8
AFTER THERAPY					
Immediately	99.7	1.26	120.0	127.5	112.6
15 to 30 min.	101.5	111.0	126.0	130.0	101.8
1 to 1.5 hr.	78.8	93.3	125.6	111.0	106.7
1.5 to 2 hr.	58.5		117.5	119.0	
2.5 to 3 hr.		72.6		114.0	
3.5 to 4.5 hr.			88.5	93.0	102.0
5 to 6 hr.				75.0	84.0

*The pressure is given as mm. Hg.

The effects of the three solutions on these two factors were observed.

A. *Glucose-Saline Solution:* There was an increase in the thyocyanate fluid and at the same time the plasma sodium concentration was reduced. In view of the failure to increase substantially the plasma volume, the increase in thiocyanate fluid must have occurred in an extravascular location.

B. *Dilute Serum:* Solution of dilute serum gave rise to a further lowering of the thiocyanate fluid.

C. *Concenterated Serum:* An increase in the thiocyanate fluid was observed in four cases and there was no change in one. The plasma sodium concentration was decreased in the former and appreciably unchanged in the latter.

Discussion: One observation in these studies seems apparent, i.e., that concentrated serum and glucose-saline solutions produced a lowering of the plasma sodium concentration. The former solution precipitated this effect at the same time that fluid was being drawn into the circulation, while in the latter case the same effect was observed when fluid was being lost from the vascular system. In both instances the thiocyanate fluid was increased. For the sake of analysis and future critical review, if one considers the thiocyanate fluid as being extracellular in location, then concentrated serum draws fluid into the extracellular compartment but mainly into the blood stream and glucose-

TABLE VI

EXPERIMENT	REMARKS	THIOCYANATE AVAILABLE FLUID (C.C.)	WHOLE BLOOD LOSS	PLASMA CO_2 COMB. POWER (VOL. %)
Wt. 9.1 kg. Conc. dog serum 77 c.c., 13.6 Gm. protein	Control	4040	57	53.4
	6.7 hr. shock	2650		25.3
	1.5 hr. after R	3360	23	31.6
Wt. 9 kg. Conc. dog serum 111 c.c., 18.4 Gm. protein	Control	4840	71	53.7
	6.5 hr. shock	3740		32.8
	1.1 hr. dose I	3880	21	43.4
Wt. 8.5 kg. 300 c.c. 5% glucose in saline	Control	2450	79	55.5
	9.5 hr. shock	1520		37.0
	0.75 hr. after R	2050	31	33.0
Wt. 10 kg. 300 c.c. 5% glucose in saline	Control	3125	57	68.0
	7.5 hr. shock	1540		41.5
	2.5 hr. after R	2140	40	37.5
Wt. 13 kg. Dilute serum 375 c.c., 14.1 Gm. protein	Control	5050	62	54.0
	9 hr. shock	4590		26.3
	21 hr. after R	4050	28	41.0
Wt. 10 kg. Dilute serum 300 c.c., 10.8 Gm. protein	Control	4040	59	
	7.5 hr. shock	3250		

Changes in sodium thiocyanate available fluid and CO_2 combining power are given. The whole blood loss represents the amount of blood removed as samples.

saline increases the same compartment but mostly outside the blood stream. A similar theoretical explanation for the action of dilute serum is more difficult, as it appears that fluid continued to escape from the extracellular area.

VI. *Effects on the Carbon Dioxide Combining Power of Plasma.*—Thirteen animals in whom the carbon dioxide combining power of plasma was determined revealed a decrease during shock amounting to an average of 36.6 per cent of the control value. Glucose-saline therapy gave rise to a further decline in the combining power accountable on the basis of dilution of the plasma. Dilute serum in larger volume also produced a further decline. Dilute serum, in smaller volume, gave rise to a slight increase in the combining power. Concentrated serum, in smaller amount, produced a decline in the combining power of a slight degree in four animals and a slight increase in one. Concentrated serum in larger amount caused an elevation in this determination varying between eight and thirteen points.

VII. *Effects on the Microscopic Appearance of Fixed Tissue Sections.*—The changes occurring in the tissues following prolonged freezing shock have been described.[1] These changes may be divided into (a) vascular: capillareo-venous stasis and small hemorrhages; (b) interstitial: edema and infiltration by neutrophilic leucocytes; and (c) parenchymatous: acute parenchymatous degeneration, focal necrosis with pyknosis, karyorrhexis, and karyolysis (liver, kidneys, suprarenal cortex). When hypotension ensued, at the time the solutions were given, these changes were generalized throughout the body.

The modifications of these findings by the three solutions used were observed. Autopsy material from seventeen dogs was studied, including five dogs from the glucose-saline group, five from the dilute serum groups, and seven from the concentrated serum groups.

In all groups the parenchymatous findings were unchanged by the therapy, parenchymatous degeneration and focal necrosis were prominent. The infiltration of pulmonary alveolar walls and suprarenal cortex by leucocytes was also unaffected. The glucose-saline group and all but one animal in the dilute serum groups displayed prominent capillareo-venous stasis, pulmonary edema, and capillary hemorrhages. The latter findings were definitely reduced following concentrated serum therapy, particularly when death occurred less than six hours after therapy. The emptying of lung capillaries and liver sinusoids was particularly evident with concentrated serum. In addition, the larger vessels contained the pink precipitate indicative of the presence of plasma fluid suspending the red cells.

COMMENT

The abnormalities occurring in freezing shock simulated the changes described in wound (traumatic) shock and other types of shock without large hemorrhages. The abnormalities included a loss of plasma fluid from the circulation averaging 52.3 per cent of the control plasma volume (3.7 per cent of body weight), hemoconcentration, hypotension, decrease in total circulating proteins, acidosis, a decrease in the thiocyanate available fluid, plasma sodium concentration, hemoglobinemia, capillareo-venous stasis, and other visceral changes. When the state of severe hypotension ensued, the re-establishment of the plasma volume improved the circulation temporarily but did not effect lifesaving recovery. The fate of glucose-saline, dilute serum, and concentrated serum in this irreversibly fatal period was observed. Concentrated serum produced an increase in plasma volume greater than the volume given, indicating a shift of fluid into the plasma stream, probably from the tissues. The shift of fluids constituted a directional flow opposite to that occurring in the pathogenesis of shock and with it there was an increase in plasma volume, hemodilution, increase in total circulating proteins, improvement of the acidosis, increase in thiocyanate available fluid, decrease in plasma sodium concentration, and a release of red cells from the capillareo-venous areas. These effects of concentrated serum were in direct proportion to the volume given.

Dilute serum in large volumes improved the circulation but at the same time fluid escaped from the vascular system in substantial volumes, protein was further lost, and capillareo-venous stasis was not substantially improved.

Glucose-saline solution was rapidly lost from the circulation and the ultimate effects were deleterious since further protein was lost and the circulatory insufficiency became more pronounced.

The comparison of dilute serum and concentrated serum on the basis of the total amount of protein administered revealed a superiority of concentrated serum over dilute serum in coping with the circulatory abnormalities in this type of shock.

CONCLUSIONS

1. The comparison of the effects of glucose-saline, dilute serum, and concentrated serum on the circulation during shock on the basis of volume given and total protein injected revealed the following ascending order of efficiency: least effective glucose-saline solution, then dilute serum smaller volume, concentrated serum smaller amount protein, dilute serum larger volume, and most effective, concentrated serum larger amount of proteins injected.

2. Concentrated serum was observed to produce consistently a shift of fluids from the tissues into the blood stream. The fluid shift reversed several of the abnormal mechanisms occurring in the capillaries.

3. The most important factor in the therapy of shock appears to be the total amount of proteins administered.

REFERENCES

1. Muirhead, E. E., Ashworth, C. T., Kregel, L. A., and Hill, J. M.: Experimental Freezing Shock, Changes in Body Fluids and Tissues, Arch. Surg. **45**: 863, 1942.
2. Muirhead, E. E., Ashworth, C. T., and Hill, J. M.: The Therapy of Shock in Experimental Animals With Plasma Protein Solutions, I. Concentrated Plasma as a Hemodiluting Agent, SURGERY **12**: 14, 1942.
3. Hill, J. M., and Muirhead, E. E.: Problems of Military Importance in the Preparation and Use of Desiccated Plasma or Serum, Texas State J. Med. **38**: 195, 1942.
4. Starling, E. H.: On the Absorption of Fluid from the Connective Tissue Spaces, J. Physiol. **19**: 312, 1896.
5. Landis, E. M.: Capillary Pressure and Capillary Permeability, Physiol. Rev. **14**: 404, 1934.
6. Cannon, W. B.: Traumatic Shock, New York, 1923, D. Appleton-Century Company, Inc.
7. Beard, J. W., and Blalock, A.: Intravenous Injections: Study of the Composition of the Blood During Continuous Trauma to the Intestines When No Fluid Is Injected and When Fluid Is Injected Continuously, J. Clin. Investigation **11**: 249, 1932.

CLINICAL EXPERIENCE WITH THROMBIN AS AN HEMOSTATIC AGENT*

R. T. TIDRICK, M.D., W. H. SEEGERS, PH.D., AND E. D. WARNER, M.D.
IOWA CITY, IOWA
(From the Departments of General Surgery and Pathology, State University of Iowa)

DURING the past four years steady progress has been made in our laboratory in the isolation and purification of prothrombin and thrombin.[1-4, 7] The probability that purified thrombin would be useful in the clinic as a hemostatic agent was a motivating factor in this work. Early clinical and laboratory studies[5, 6] with some of our purified material were so encouraging that the data were presented to the research department of Parke, Davis & Co. With the aid of extensive production facilities, that company has undertaken to produce thrombin in quantity sufficient to ensure more complete clinical and experimental studies. It is our present purpose to present a brief summary of clinical results obtained with thrombin which we have received from this source.

THE PRODUCT THROMBIN AND MODE OF APPLICATION

The thrombin preparation, "Thrombin Topical,"† is a white powder. Its sterility has been proved repeatedly by cultures made both aerobically and anaerobically. Each vial contains approximately 10,000 units (the thrombin unit is defined[2] as that amount required to clot 1 c.c. of standard fibrinogen solution in fifteen seconds).

The sealed vial containing the sterile thrombin powder is sterilized by immersion in antiseptic solution. We have placed the vials in Bard-Parker solution for ten minutes. Before opening the vial it is rinsed with water to remove the antiseptic solution, for if the latter were to gain entrance to the vial the thrombin would be weakened. On addition of 10 c.c. of sterile water the thrombin dissolves promptly and completely. At this concentration, approximately 1,000 units per c.c., the thrombin solution causes clotting of an equal volume of human blood in less than one second. It will clot ten times this volume within three seconds, or 1,000 times its volume in twenty-three seconds.

In applying the thrombin solution to the bleeding surfaces, a spray is useful, but a syringe and fine needle are generally sufficient to flood the surface. Uniform and rapid covering of the entire surface is often facilitated by the simple expedient of gently rubbing the surface with

*Aided by a grant from the John and Mary R. Markle Foundation.
†The thrombin used was supplied by Parke, Davis & Co.
Received for publication Feb. 20, 1943.

the gloved finger. The use of gauze to wipe the surface has the disadvantage of breaking up the clot as it forms and also of removing any excess thrombin solution before it has had time to act fully. The wound should, however, be relatively free of blood at the time the thrombin is applied. If a thick layer of blood is present on the surface, the thrombin tends to clot merely the surface layers and the bleeding continues underneath the clot. Firm anchorage of the clot occurs most readily when the emergent blood is allowed to mingle with the thrombin the moment it reaches the surface. It is important to bear in mind that the hemostatic effect of thrombin is dependent, in large measure, upon the clot which forms in and on the surface of the bleeding tissues, rather than upon the formation of thrombi in the vessels in the depth of the tissues. For this reason, it is essential that the hemostatic clot be left in place. Undue sponging, to remove the clot, disrupts its anchorage and oozing often begins again. We believe that in most cases no harm results from leaving thin films of clotted blood in place. In fact, the thin clot, which forms subsequently in any event, is actually essential to fibroblastic repair rather than detrimental.

Application of the dry thrombin powder, though more wasteful of the thrombin preparation, is also effective, and at times, a more convenient method of application. We have used the dry powder, particularly in certain bone operations in which deeply situated bleeding surfaces were to be closed tightly, immediately. In wounds of this type, the dry powder, which can be rubbed into the surfaces, has the advantage of avoiding the introduction of any fluid deep into the wound and permits tight closure without danger of seepage.

The use of cotton pledgets or bits of gauze saturated with the thrombin solution is at times a convenient method of application, but, in general, this method does not give satisfactory results. The clot which forms is firmly anchored in the cotton, and when the latter is removed, more often than not, the clot is disrupted from its anchorage in the tissue with the result that the bleeding is reinitiated.

CLINICAL RESULTS

Thrombin has been employed for its hemostatic effect in somewhat over 225 cases in the University Hospitals. In these cases, the bleeding has varied widely, both in type and in the difficulty with which it could be controlled by ordinary means.

The largest and most uniform group consisted of 102 cases in which we have used thrombin to control operative bleeding from donor skin graft sites. We have found the thrombin to be of especial aid on the denuded surfaces following removal of split-thickness sheet grafts. Many of the patients in these cases bleed rather profusely at the time of operation and ooze into the dressings afterward. A considerable number of these patients are chronically debilitated and we believe the

prevention of blood loss here is a definite factor in reducing both operative morbidity and mortality. In a total of seventy-eight split-thickness grafting operations of this type the results have been very gratifying. In forty of the cases complete hemostasis was obtained in a few minutes and although rather bulky clots formed in some patients, there was no significant postoperative bleeding. In thirty-two cases there was immediate cessation of oozing with the formation of a uniform, thin clot and no subsequent bleeding into the dressings. There were only two cases in which the thrombin appeared to have little effect, and pressure was needed to control fully the initial oozing.

Thrombin was used twenty-four times in conjunction with pinch graft donor areas. The results in these were excellent in six cases, satisfactory in thirteen, fair in four cases, and in one case, hemostasis was not obtained with the thrombin. Since the central portion of the pinch graft extends through the total thickness of the skin, small arteries are occasionally encountered which require other hemostatic measures. In general, hemostasis was effected less promptly and with the formation of more bulky clots in this type of case than in the split-thickness type of graft.

In twenty-seven cases, thrombin has been employed in the control of operative bleeding from cancellous or cortical bone. In fifteen instances the hemostasis was prompt and complete. In seven cases, hemostasis was somewhat less prompt but was considered satisfactory by the operator. In only two of the cases did the thrombin fail to check the bleeding. In the remaining two cases the results were indeterminate due to simultaneous employment of other hemostatic measures. In many cases of stubborn oozing from the cut surface of bone, the effect of the thrombin has been very dramatic and has obviated the undesirable plugging of the cancellous bone spaces or haversian canals with bone wax or other foreign bodies. In the control of bleeding from bone we have generally used the thrombin in solution, but in many instances have found the dry powder more convenient.

When a tourniquet is employed in operations on the extremities it is usually desirable to release the constrictor, at least temporarily, before applying thrombin. By so doing, larger vessels may be recognized and ligated. If the thrombin solution is applied first, these vessels may be held temporarily in check, only to resume serious bleeding after the wound is closed.

During cholecystectomy persistent oozing from the gall bladder bed is occasionally very difficult to control. We have used thrombin in two such cases in which suture ligatures were ineffectual. Application of the thrombin to the profusely oozing surfaces brought about prompt clotting and effectively checked the bleeding. In a third similar case, complete hemostasis was not obtained until additional ligatures were placed. Animal experiments[5, 6] indicate that the thrombin may also be of great aid in operations upon the liver itself.

We have found thrombin to be a useful adjunct in two cases for the control of the oozing of the cut margin of the pylorus in the Rammstedt pyloroplasty procedure.

The surgeon not infrequently encounters difficulty in obtaining satisfactory hemostasis incident to drainage, excision, or débridement in areas of acute or chronic inflammation. This is particularly true when the procedure is associated with trauma to friable granulation tissue or when there are many small bleeding vessels situated in dense scar tissue. In twenty-seven operative procedures in wounds falling in these categories, the results have been very gratifying in all but two cases. We have also used thrombin to control oozing at the mucocutaneous margin, or where there was mild bleeding at the margin of the eschar, in hemorrhoidectomy operations of the clamp and cautery type. Its use was considered efficacious on three of the four occasions applied.

Thrombin has been used in nine patients to control oozing from mastectomy skin flaps with good hemostasis in seven instances. The results were somewhat equivocal in the other two cases. There is some evidence that its use may reduce the incidence of postoperative fluid collections beneath the flaps and play a part in promoting early agglutination and healing.

Thrombin has been used in six patients with various forms of blood dyscrasia, following biopsy or traumatic wounds. In three of these, excellent hemostasis was obtained. In the fourth case, a patient with an undiagnosed bleeding tendency, the thrombin appeared to have little effect. In the fifth case thrombin was used on two occasions but without definite benefit. In a second undiagnosed dyscrasia with a bleeding ulcer of the lip the results were good on two occasions. On one occasion, the bleeding point could not be reached with the thrombin and hemostasis was not effected.

In eight cases of delayed postoperative bleeding the thrombin has proved to be very helpful in five, of some aid in one, and of no definite benefit in another. In this latter case, there was a small artery in the depths of the wound, and it was necessary to reopen the wound and ligate this vessel before the bleeding could be checked. In this type of case, thrombin can sometimes be introduced into a bleeding sinus or tract by means of a small catheter, and thus minimize the need for disrupting the wound in order to obtain hemostasis. Care must of course be taken to see that the thrombin is never injected intravenously.

We have had occasion to use thrombin to control bleeding from ulcerated neoplasms in five instances. In all of these hemostasis was effected. In two of the cases, there had been large blood loss preceding this measure and the usual hemostatic measures had failed.

Thrombin has been utilized in some thirteen or more miscellaneous cases of soft-tissue bleeding associated chiefly with operative wounds. In several of these, the bleeding was so trivial as to make analysis of

the usefulness of thrombin difficult, but in at least nine of these cases it has been thought by the operator to be of definite aid.

All cases were studied closely to detect the existence of thromboses, but all were negative in this respect. In earlier work[5, 6] this problem of thrombosis was studied experimentally in rats and dogs. Thrombin in large amounts was injected directly into soft tissues. In no case was there any evidence of thrombosis in the vessels nearby. The direct injection of thrombin into human tissues would probably be harmless also, but we have avoided this procedure for fear that the thrombin might be injected accidentally into a vein. From animal experiments[5, 6] the intravenous injection of thrombin is known to cause widespread thrombosis.

The postoperative course of the wounds treated with thrombin was carefully recorded, with special attention to any suggestion that the thrombin produced local irritation. In no case was there any evidence of this. Infected wounds showed no more redness or suppuration than ordinarily exists. Clean wounds healed promptly by primary intention without any evidence that the thrombin had caused irritation. Even when the thrombin was applied repeatedly over a period of many weeks, there was no evidence to indicate the development of hypersensitivity. We were particularly interested in this, for the thrombin is prepared from beef plasma and might be expected to act as a foreign protein in this respect.

The use of large amounts of the sulfonamide group of drugs in the wounds is not a contraindication to the simultaneous use of thrombin, nor do the drugs interfere with the hemostatic action of the thrombin preparation.

SUMMARY

Experience with the hemostatic effects of "Thrombin Topical" in a wide variety of cases indicates that it provides a very useful adjunct to surgical technique. In general, oozing of blood from capillaries and small venules can be checked promptly whenever the bleeding surfaces are accessible. Even in the case of small arteries application of thrombin is often effective, particularly if digital pressure can be applied to the bleeding points momentarily in order to permit the clot to become firmly anchored in the tissue.

There has been no evidence that the thrombin produced local irritation nor that patients, in whom the preparation was used repeatedly, became hypersensitive to it. None of the patients showed evidence of untoward effects from absorption of the thrombin, or from local thrombosis of vessels.

In approximately one-half of the cases the operative work was done by one of us (R. T. T.). For the remainder of the cases, we are indebted to other members of the Department of General Surgery and to the Orthopedic Surgical staff, especially Dr. L. A. Williams.

Since this report was submitted for publication, we have found thrombin to be particularly useful for control of the oozing of blood from brain tissue.

REFERENCES

1. Seegers, W. H., Smith, H. P., Warner, E. D., and Brinkhous, K. M.: The Purification of Prothrombin, J. Biol. Chem. **123**: 751-754, 1938.
2. Seegers, W. H., Brinkhous, K. M., Smith, H. P., and Warner, E. D.: The Purification of Thrombin, J. Biol. Chem. **126**: 91-95, 1938.
3. Seegers, W. H.: Purification of Prothrombin and Thrombin: Chemical Properties of Purified Preparations, J. Biol. Chem. **136**: 103-111, 1940.
4. Seegers, W. H.: The Purification of Prothrombin, J. Biol. Chem. **140**: 677, 1941.
5. Seegers, W. H., Warner, E. D., Brinkhous, K. M., and Smith, H. P.: The Use of Purified Thrombin as an Hemostatic Agent, Science **89**: 86, 1939.
6. Warner, E. D., Brinkhous, K. M., Seegers, W. H., and Smith, H. P.: Further Experience With the Use of Thrombin as a Hemostatic Agent, Proc. Soc. Exper. Biol. & Med. **41**: 655-657, 1939.
7. Seegers, W. H.: Further Purification of Thrombin: Probable Purity of Products, J. Biol. Chem. **146**: 511-518, 1942.

METABOLIC STUDIES IN PATIENTS WITH CANCER OF THE GASTROINTESTINAL TRACT

VI. Disorders in Alimentary Digestion and Absorption in Patients Who Have Undergone Total Gastrectomy for Carcinoma of the Stomach*

P. E. Rekers, M.D.,† George T. Pack, M.D., and C. P. Rhoads, M.D., New York, N. Y.

(From the Memorial Hospital for the Treatment of Cancer and Allied Diseases New York)

DURING the past twenty years steady progress has been made in the postoperative care of patients who have undergone surgical treatment for diseases of the alimentary tract. Patients who have undergone total gastrectomy, however, uniformly have had a difficult postoperative course. Even after a survival period which would be expected to be adequate, these patients seldom returned to their original weight. They complained of intestinal disorders, developed anemia, and, occasionally, evidence of vitamin deficiencies. The investigation here reported was undertaken to ascertain whether or not the cause of these disorders in patients after total gastrectomy is to be found in an abnormal digestion of simple dietary constituents.

Previous metabolic studies following gastric resection for ulcer and carcinoma of the stomach do not show uniform results but some of these studies indicate an excess of fat in the stools.[1, 2] However, many of these studies were carried out with inadequate quantitative methods. In general, previous investigators concluded that the stomach could be removed from animals and from man without seriously incapacitating the individual.[1-4]

CLINICAL MATERIAL

This report is based on the results of study of four different groups of patients. The first is composed of eight individuals who were used as controls. They were admitted to the hospital for treatment of disorders entirely unrelated to the gastrointestinal tract. There was no reason to believe that any of them had ever had gastrointestinal disease. Two of these eight control subjects received diets identical with those given to the patients following total gastrectomy. The remaining six received routine hospital diets which contained daily approximately 80

*The authors gratefully acknowledge the assistance given by the Jane Coffin Childs Memorial Fund for Medical Research, The Standard Brands, Inc., and the National Cancer Institute Fund.

†Trainee in the diagnosis and treatment of cancer, National Cancer Institute.

Received for publication, Dec. 5, 1942.

Gm. of fat, 18 Gm. of protein nitrogen, and 175 Gm. of carbohydrate. It is to be noted that the amount of fat they ingested is twice that fed to the patients who had undergone total gastrectomy.

The second group is composed of three patients who had undergone total gastrectomy for carcinoma of the stomach and had survived the operation for more than six months. At the time of observation they were free from evidence of neoplastic disease. The case histories of these three patients are presented in detail in a subsequent section of this communication.

A third group is represented by one patient who had undergone a partial gastrectomy for carcinoma of the prepyloric region of the stomach and still secreted considerable quantities of both free and combined hydrochloric acid.

A fourth group is represented by one patient bearing a carcinoma of the prepyloric region of the stomach. The growth was deemed inoperable because it was adherent to the pancreas and large vessels posteriorly. There was no gross evidence of metastasis.

METHODS AND CRITERIA

Metabolic studies were not made on any patient until the basal diet had been taken for at least three days and, in the case of the patients who had undergone gastrectomy, at least one week. No vitamins or treatment for anemia had been administered for at least two months. The patients who had been subjected to total gastrectomy had survived their operation for at least six months and were still free from evidence of neoplastic disease.

The diets given to two of the patients in the control group, to all of those that had undergone total gastrectomy, to the one that had undergone partial gastrectomy, and to the one who bore a gastric cancer were analyzed diets in which a constant source of meat was used. The diets of the remaining patients in the control group have been described previously.[1] The excreta were collected from one- to four-day periods, the nitrogen and fat contents calculated on a per diem basis. Multiple periods of study were used in most instances.

Methods for the chemical analysis and vitamin assay of blood and excreta have been described in the previous publications of this series.[5, 6, 7]

RESULTS

The results of the experiments herein described may be grouped under three headings:

1. Studies of the excretion of fat and nitrogen by a control group of patients and by patients who have had a total resection of the stomach for carcinoma.

2. Experiments to determine the nature and the cause of the faulty digestion and absorption of dietary constituents in patients who have had total resection of the stomach for carcinoma.

3. A study of the hematologic picture of those patients who have had total resection of the stomach for carcinoma.

Metabolic studies in a control group of patients and in those who have had total resection of the stomach for carcinoma.—The daily fecal excretion of fat by the eight individuals used as controls was measured in fifty-four specimens of stool collected in periods of from one to four days. The fat* content of these specimens varied from 1.0 to 6.5 Gm. per day. The average excretion of fecal fat by each individual ranged from 2 to 6 Gm. per day (Table I).

The fecal outputs of nitrogen were determined in fifteen stool specimens excreted by four of the control individuals. The collection periods were from one to four days, each, in duration. The nitrogen content of the specimens varied from 0.6 to 1.5 Gm. per day and the average daily fecal excretion of nitrogen varied from 0.7 to 1.5 Gm. These values for fecal fat and nitrogen are in good agreement with those reported by others[8] (Table I).

TABLE I

DIETARY INTAKE AND FECAL AND URINE EXCRETION IN A CONTROL GROUP OF PATIENTS

PATIENT	DISORDER	TYPE OF DIET	DIET PER DAY		FECES PER DAY			URINE PER DAY
			FAT (GM.)	NITROGEN (GM.)	FAT (GM.)	FAT EXCRETED (PER CENT)	NITROGEN (GM.)	NITROGEN (GM.)
A. F.	Hemangioma of foot	(a)	35	11.2	3	9	0.7	10.1
A. D.	Oral leucoplakia	(a)	35	10.1	4	13	0.9	9.0
P. R.	Varicose veins	(c)	105	14.4	4	4	0.8	15.0
F. P.	Plantar wart	(c)	135	16.0	6	4	1.5	14.6
A. S.	Osteitis fibrosa cystica	(d)	75	18.0	2	3		
H. Z.	Chronic lymphatic leucemia	(d)	75	18.0	3	4		
I. D.	Xeroderma pigmentosa	(d)	50	12.0	3	6		
F. B.	Arrested amoebiasis	(d)	75	18.0	3	4		

(a) Analyzed diet.
(c) Calculated diet.
(d) Regular hospital diet.

In distinct contrast to the findings in the control group were those obtained from study of the three patients who had undergone total gastrectomy. Stool and urine collections were made for thirteen basal periods, each of which lasted from three to four days. During these periods the patients were found to excrete daily from 8 to 50 Gm. of fat. The average excretion of fecal fat by each individual ranged from 11 to 23 Gm. per day. It is interesting to note that whereas the control patients who ingested from 35 to 80 Gm. of fat never excreted more than 6 Gm. per day, these individuals without stomachs never

*In the present communication the term "fat" is used to express the stearin equivalent of the stool.

TABLE IIA

DIETARY INTAKE AND FECAL AND URINE EXCRETION IN PATIENTS WHO HAVE UNDERGONE TOTAL GASTRECTOMY FOR CARCINOMA

PERIOD	DIET PER DAY		FECES PER DAY			URINE PER DAY
	FAT (GM.)	NITROGEN (GM.)	FAT (GM.)	FAT EXCRETED (PER CENT)	NITROGEN (GM.)	NITROGEN (GM.)
Patient D. S. (a)						
Basal	50	4.0	12	24	1.0	3.1
High fat	100	4.5	13	13	0.8	2.8
High protein	50	17.1	8	16	1.1	8.6
Patient J. C. (a)						
Basal	70	12.4	11	16	1.3	9.8
High fat	125	14.6	12	10	1.7	9.2
High protein	75	23.2	7	9	1.7	9.5
Oral liver extract (b)	70	11.0	6	8	1.2	9.5
Patient A. Z. (a)						
Basal	40	10.0	23	57	2.2	8.8
Fat free (start)	2	10.0	19	100+	3.4	7.3
Fat free (end)	2	10.0	7	100+	2.6	7.0
Basal (after fat free)	40	10.0	38	95	3.0	9.2
Gelatin	40	18.6	30	75	2.6	18.0
Beef	60	16.0	28	47	4.2	16.1
Lipocaic	40	10.0	26	65	2.7	10.3
Pan. enzymes (start)	40	10.0	37	93	2.8	10.7
Pan. enzymes (end)	40	10.0	8	20	1.2	11.9
High fat	220	10.0	125	57	6.8	9.3
Ventriculin	40	10.0	28	70	1.9	18.8
Liver extract crude (intramuscular) (c)	40	10.0	17	14.3	2.2	11.2
Bile salts	40	10.0	33	80	5.0	7.1

(a) Analyzed diet.
(b) Eli Lilly and Company.
(c) Eli Lilly and Company, No. 370.

excreted less than 8 Gm. of fat per day although they ingested only 40 Gm. of fat (Table IIA).

The patients who had undergone total gastrectomy excreted in their stool from 0.8 to 3.3 Gm. of nitrogen per day and, in their urine, from 5.3 to 14.4 Gm. of nitrogen per day. The average excretion of fecal nitrogen by each individual ranged from 1.0 to 2.2 Gm. per day. The values of fecal nitrogen excretion in two of these three individuals were within normal range of less than 1.5 Gm. per day. The third individual (A. Z.) excreted from 1.3 to 3.3 Gm. of nitrogen per day in his stool, values distinctly above the normal range (Table IIA). From these results it is apparent that all three patients who had undergone total gastrectomy manifested a conspicuous steatorrhea and one of these three patients manifested a conspicuous creatorrhea.*

Experiments to ascertain the source and nature of the faulty digestion and absorption of the dietary constituents.—

A. Are the steatorrhea and creatorrhea of those patients without stomachs of intrinsic or extrinsic origin? In order to determine whether or

*Creatorrhea used to indicate excess fecal nitrogen.

TABLE IIB

TABULATION OF BLOOD COUNT AND SERUM PROTEIN CONCENTRATION IN PATIENTS WHO HAVE UNDERGONE TOTAL GASTRECTOMY FOR CARCINOMA

PERIOD	RED BLOOD CELLS (MILLIONS)	HEMOGLOBIN (PER CENT)	LEUCOCYTES	HEMATOCRIT (PER CENT)	MEAN CORPUSCULAR VOLUME (CU. MICRONS)	RETICULOCYTES (PER CENT)	SERUM PROTEIN		
							TOTAL (GM. PER CENT)	ALBUMIN (GM. PER CENT)	GLOBULIN (GM. PER CENT)
Patient D. S. (a)									
Basal	4.2	88	5,400	35	83	0.8	6.3		
High fat	4.1	91	7,750			0.6	7.5		
High protein (beef)	3.8	91	5,000	33	87	0.8	6.4		
Patient J. C. (a)									
Basal	3.9	76	8,200	31	81	1.2	6.7		
High fat	3.9	78	6,950	32	82	1.0	6.6		
High protein (beef)	3.5	76	6,500	33	92	1.2			
Oral liver extract (b)	3.5	72	7,700	33	92	1.8	6.5		
Patient A. Z. (a)									
Basal	4.6	96	6,300	43	93	0.8	7.3	4.8	2.5
Fat free (start)	3.8	77	4,300	39	104	0.8	6.4	4.6	1.8
Fat free (end)	4.0	82	5,000	35	88	0.6	6.8		
Basal (after fat free)	4.1	85	6,250	35	84	0.6	6.6		
High protein (gelatin)	3.8	80	4,500	32	84	1.0	6.6		
High protein (beef)	4.1	84	5,000	37	90	0.8	6.4	4.7	1.7
Lipocaic	4.1	87	5,100	39	90	0.7	6.8	4.7	2.1
Pancreatic enzymes (start)	4.1	84	4,700	35	85	0.8	6.9		
Pancreatic enzymes (end)	3.8	74	5,400	33	88	1.0	7.3		
High fat	4.2	85	5,800	37	89	0.8	6.5	4.3	2.2
Ventriculin	4.0	82	5,200	39	98	0.6	6.9	4.9	2.0
Liver extract crude (intramuscular) (c)	4.1	83	4,900	37	90	0.8	6.8	4.7	2.1

(a) Analyzed diet.
(b) Eli Lilly and Company.
(c) Eli Lilly and Company, No. 370.

not the steatorrhea and creatorrhea were of dietary origin, it was necessary to vary the dietary fat and protein intake, respectively, and to note any associated changes in the steatorrhea and creatorrhea. Accordingly, one patient, A. Z., was placed on a fat-free diet for fourteen days. This regime of the fat-free diet was associated with a pronounced decrease in the steatorrhea. The stool fat outputs fell from 39 to 7 Gm. per day, a value within the normal range. There was no significant change in the fecal excretion of nitrogen (Table IIA).

The subsequent daily addition of 40 Gm. of fat to the fat-free diet of patient A. Z. was followed by an immediate rise in the fecal fat excretion from 7 to 38 Gm. per day and by no appreciable alteration in the fecal nitrogen output. Furthermore, the addition of a single feeding of 180 Gm. of fat in the form of butter and cream to the basal diet which contained 40 Gm. of fat resulted in the excretion of 125 Gm. of fat and 6.8 Gm. of nitrogen in the stool during the next twenty-four-hour period (Table IIA).

The daily addition of from 40 to 60 Gm. of dietary fat in divided feedings in the form of butter to the basal diet of the remaining two patients resulted in no significant change in either the fecal excretion of fat or nitrogen (Table IIA).

From the results it would appear that in one individual who had a severe steatorrhea, this abnormality was directly related to the amount of fat ingested. The creatorrhea in this patient was related not only to the dietary protein but also to the dietary fat, since it increased with the increased intake of fat. The results are in agreement with the findings of others who studied the fat absorption in patients with idiopathic steatorrhea.[9]

B. Cause of the steatorrhea and creatorrhea: The more probable explanations for the steatorrhea and creatorrhea were considered to be: (1) absence of the stomach; (2) disturbances of alimentary digestion and absorption because of the previously existing cancer of the stomach; (3) deficient biliary secretion; (4) deficiency of an unknown pancreatic factor of an exocrine nature (such as lipocaic); (5) lack of an adequate secretion of pancreatic enzymes into the intestines; (6) diets deficient in protein; and (7) insufficient amounts of an unknown substance called an extrinsic factor as found in liver extract.

(1) Absence of the stomach. Since the stomach provides gastric chyme, an intrinsic factor in the gastric juice, serves as a reservoir for recently ingested food, and regulates the flow of food into the intestines, it was important to determine if any of these factors were the cause of the steatorrhea and creatorrhea in the patients investigated. Accordingly, one patient was selected for study who had undergone partial resection of the stomach for cancer of that organ and still retained adequate amounts of both free and combined hydrochloric acid. Over one-third of the stomach was free of evidence of neoplastic disease. This patient (E. P.) was found to have a steatorrhea, the out-

puts ranging from 13 to 18 Gm. and averaging 16 Gm. in the daily fecal excretion. No creatorrhea existed (Table IV). Furthermore, the daily addition of 35 Gm. of a substance* potent in the intrinsic factor, for ten days, to the basal diet of patient A. Z. with total gastrectomy, failed to alter the existing severe steatorrhea (Table IIA).

TABLE III

DIETARY INTAKE AND FECAL AND URINE EXCRETION IN A PATIENT BEARING GASTRIC CANCER

PERIOD	DIET PER DAY		FECES PER DAY			URINE PER DAY
	FAT (GM.)	NITROGEN (GM.)	FAT (GM.)	FAT EXCRETED (PER CENT)	NITROGEN (GM.)	NITROGEN (GM.)
Patient A. Z.						
Basal (a)	50	10	8	16	1.6	7.3
Basal (c)	90	14	5	10	1.1	8.0
High fat	230	14	16	7	1.6	7.7

(a) Analyzed diet.
(c) Calculated diet.

TABLE IV

DIETARY INTAKE AND FECAL AND URINE EXCRETION IN A PATIENT WHO HAD UNDERGONE PARTIAL GASTRECTOMY

PERIOD	DIET PER DAY		FECES PER DAY			URINE PER DAY
	FAT (GM.)	NITROGEN (GM.)	FAT (GM.)	FAT EXCRETED (PER CENT)	NITROGEN (GM.)	NITROGEN (GM.)
Patient E. P.						
Basal (a)	35	10	16	45	1.3	5.8

(a) Analyzed diet.

In addition, small jejunal pouches or reservoirs of approximately 200 ml. capacity were demonstrated by roentgenography in the two patients (J. C. and D. S.) studied, while increased motility of the intestines was not demonstrated by fluoroscopic studies in any patient in this series.

No further evidence seemed necessary, therefore, to establish beyond reasonable doubt that the steatorrhea as noted in these patients without a stomach was not due to a lack of gastric chyme, an intrinsic factor in the gastric juice, sufficient reservoir to hold the ingested food nor increased intestinal motility.

(2) Previous existence of cancer. It may be assumed that the previously existing cancer of the stomach altered the gastric mucosa and resulted in defective digestion and absorption of the dietary constituents, fat in particular. Hence, it became important to determine whether or not a steatorrhea and creatorrhea existed in a patient who bore a carcinoma of the stomach. Accordingly, a patient was selected for similar

*Ventriculin.

study who bore a carcinoma of the stomach but no evidence of metastases, gastric obstruction, bleeding, or pyrexia.

Stool and urine collections were made on this patient for nine periods of from one to four days each, during which a basal diet was fed. For the first four periods the basal diet was exactly the same as that fed to the patients with total gastrectomy. This diet contained 50 Gm. of fat, 11 Gm. of protein nitrogen, and 300 Gm. of carbohydrate. During the next five periods the basal diet contained 90 Gm. of fat, 14 Gm. of protein nitrogen, and 180 Gm. of carbohydrate.

During the basal periods the patient excreted daily from 5 to 9 Gm. of fat, from 1.0 to 1.8 Gm. of nitrogen in the stool, and from 5.4 to 7.2 Gm. of nitrogen in the urine. His oral glucose tolerance test was normal. The average daily fecal excretion of fat was 6.0 Gm. and of nitrogen was 1.0 Gm. Thus, this individual with carcinoma of the stomach in situ presented findings essentially in keeping with the findings obtained in the control group of patients (Table III).

It would appear, therefore, that the presence of the cancer does not play a direct mechanical role in disturbing the digestion and subsequent absorption of the dietary protein and fat.

(3) An inadequate supply of bile in the intestine. Since the presence of bile in the intestine is considered to be essential for the proper digestion and absorption of fat, it became necessary to consider an inadequate supply of bile as a causative factor for the steatorrhea in the patients without stomachs.

None of these patients in the present study who underwent total gastrectomy showed evidence of biliary tract disease at the time of operation, nor was the biliary tract interfered with surgically. All stool specimens presented gross evidence of bile pigment at all times. Finally, in one patient (A. Z.), the addition of 4 Gm. of bile salts per day to the diet caused abdominal cramps, accentuation of the loose bulky stools, and an increase of the daily stool fat output from 22 to 33 Gm. and an increase of the nitrogen output from 3.3 to 5 Gm. Therefore, further evidence was not deemed necessary to indicate that an inadequate supply of bile was a cause for the existing steatorrhea (Table IIA).

(4) Insufficiency of pancreatic hormone. Inasmuch as abnormal lipid metabolism with excess fatty infiltration of the liver has been ascribed to a deficiency of a pancreatic hormone,[10] such as lipocaic, it became desirable to determine whether or not such a hormone deficiency was related to the steatorrhea in the patients under study.

Six grams of lipocaic were administered daily for ten days to one patient (A. Z.) who had a conspicuous steatorrhea without appreciable alteration in the existing steatorrhea and creatorrhea (Table IIA).

Thus, it appeared that the steatorrhea and creatorrhea were not caused directly by a deficiency of the pancreatic hormone, lipocaic.

(5) Insufficiency of pancreatic enzymes. Pancreatic enzymes have been demonstrated repeatedly to be necessary for the proper utilization

of dietary fat and protein in animal and man,[11, 12] and their absence must be considered among the possible causative factors for the steatorrhea in the patients under consideration. However, in none of the three patients who underwent gastrectomy was organic disease of the pancreas demonstrable at the time of operation and none had their pancreatic ducts ligated. Two of these three patients showed no evidence of creatorrhea, hence their digestion and absorption of the dietary protein were probably adequate (Table IIA).

The daily administration to one patient (A. Z.) of 25 Gm. of pancreatic enzymes, a dose found to be effective in pancreatic insufficiency,[13] was found to reduce the fecal output of fat from about 20 to 8 Gm. per day and the fecal nitrogen from 2.8 to 1.2 Gm. daily. These findings indicated that the steatorrhea and creatorrhea might be related to either an insufficiency of the fat and protein-splitting enzymes or to an improper mixing of the intestinal contents with their pancreatic enzymes (Table IIA).

(6) An adequate supply of dietary protein. Inasmuch as some observers believe that protein restriction in the diet results in a decreased utilization of the dietary fat,[14] it was important to exclude as a causative factor for the steatorrhea an insufficient supply of dietary protein. Accordingly, in two of the three patients, the basal diet was supplemented with from 70 to 80 Gm. of protein in the form of cooked beef for a period of fourteen days each. During the period in which the beef supplement was administered, there was a reduction in the average daily fecal fat excretion from 11 and 12 Gm. to 7 and 8 Gm., respectively, fat outputs close to the normal range. Furthermore, such protein supplements were not associated with any appreciable changes in the fecal nitrogen excretion.

Since beef is a complex dietary protein and contains appreciable amounts of choline, a substance with known lipotropic activity, it became desirable to employ a protein supplement free from such lipotropic material. Accordingly, the third patient (A. Z.) received 100 Gm. of gelatin as his protein supplement for fourteen days. No appreciable change in the degree of his steatorrhea or creatorrhea followed. Furthermore, when the gelatin was replaced for fourteen days with 100 Gm. of cooked beef there was no appreciable change in the steatorrhea, but the fecal excretion of nitrogen rose from 2.7 to 4.2 Gm. per day (Table IIA).

The findings in two patients of an apparent fat-sparing action of dietary protein for dietary fat were not confirmed in the third patient. These results deserve confirmation and further study.

(7) Insufficient quantities of extrinsic factor. Patients with tropical sprue and intestinal anastomosis and strictures frequently manifest steatorrhea, which in many instances may be alleviated by the administration of large quantities of crude liver extract.[15, 16] In order

to ascertain whether or not the steatorrhea in the patients without stomachs was due to a lack of such a substance as an extrinsic factor which is found in liver extract, one patient (A. Z.) was given 5 ml. of crude liver extract intramuscularly daily for fourteen days. No appreciable alteration in the fecal excretion of fat or nitrogen followed. A second patient, without a stomach (J. C.), was fed 12.8 Gm. of liver extract orally daily for twelve days. No significant change occurred in this patient (J. C.) in the fecal excretion of fat and nitrogen which were within the normal range at that time. From these studies, therefore, it does not appear that the existing steatorrhea was affected by the administration of liver extract (Table IIA).

From the evidence at hand, it was possible to conclude only that the steatorrhea in these patients who had undergone total gastrectomy was related directly to the dietary fat, possibly related to the protein content of the diet, and probably related to fat-splitting enzymes found in the pancreas.

The creatorrhea, as noted in one patient only, is related not only to the dietary protein but also to the dietary fat.

A study of the hematologic picture of those patients who have had a total gastrectomy for carcinoma of the stomach.—Since various derangements of the stomach such as achlorhydria and mucosal changes have been found to be associated frequently with a macrocytic anemia,[17] it became important to determine if those patients who had undergone total gastrectomy manifested alterations in blood formation. Accordingly, weekly studies were made on the circulating blood of each patient in the present study to ascertain the hematologic picture. Anemias were demonstrated in each of the three patients that had undergone total gastrectomy (Table IIB). The anemias were of varied degrees but all essentially of the normochromic, normocytic type. A persistent macrocytic anemia was not present in any patient.

A. Causes for the anemia: The more probable causes for the anemias were considered to be:

(1) The patients lacked an extrinsic factor as found in liver extract or an intrinsic factor as found in the normal stomach.

(2) The patients were deficient in dietary protein.

(3) The patients harbored an infection.

(4) The patients had a disturbance of bone marrow function.

(5) The patients suffered from disturbances of alimentary digestion and absorption.

(6) The patients had a blood loss or increased blood destruction.

(1) Extrinsic and intrinsic factors. Since substances containing an extrinsic factor have been found to be effective in the treatment of certain deficiency anemias,[18] it was important to determine whether or not the anemia in the patients in the present study was due to a deficiency of a principle as found in liver extract. Therefore, one patient (A. Z.) was given 5 ml. of crude liver extract intramuscularly, daily for four-

teen days, and a second patient (J. C.) was given 12.8 Gm. of liver extract orally, daily for twelve days without any significant alteration in the blood picture in either patient (Table IIB).

Likewise, since an intrinsic factor from the stomach has been found to be effective in the treatment of certain deficiency anemias,[19] it became desirable to determine whether or not the anemia of the patients who had undergone gastrectomy was due to a deficiency of such a principle as found in ventriculin. Accordingly, the basal diet of patient A. Z. was supplemented with 33 Gm. of a substance potent in the intrinsic factor* daily for ten days without alteration in the existing anemia (Table IIB).

From this evidence it does not appear that a deficiency of either the intrinsic or extrinsic factors was the cause for the anemia in those patients studied.

(2) Dietary protein. It has been well established that hemoglobin production in anemia can be controlled by diet;[20] more specifically, that iron and protein stores or intake are the essential factors. Meats have been shown to be potent in these diet factors that are necessary for hemoglobin formation.[20] With these fundamental concepts in mind the basal diet of each of the patients who had undergone gastrectomy was supplemented with 100 Gm. of beef daily for at least fourteen days. Such feedings, however, were not associated with any significant alteration in the existing anemia (Table IIB).

Thus, it did not appear that a deficiency of dietary protein was the causative factor for the anemia in those patients who had undergone total gastrectomy.

(3) Infection. Since the presence of infection may profoundly influence hemoglobin production, in spite of adequate dietary protein,[20] it became desirable to exclude such an inhibiting factor as a possible cause for the anemia in those patients who had undergone total gastrectomy. A careful search in each instance failed to reveal the presence of an infection.

(4) Marrow function. Inasmuch as the hematologic picture may be altered by disturbances in function of the bone marrow,[21] it became necessary to investigate, when possible, the bone marrows of these individuals who had undergone total gastrectomy. Microscopic study of the sternal marrow of patient A. Z. revealed an essentially normal picture. Patient D. S. was reported to have died with evidence of metastatic carcinoma in the bones of the skull, cervical vertebrae, and pelvis.

From this evidence it is possible that one patient in this study manifested an anemia because of alterations in the function of the bone marrow.

(5) Alimentary digestion and absorption. Finally, the anemia in the patients in this study might be considered to be due to a disturbance in alimentary digestion and absorption. To examine this possibility,

*Ventriculin.

the excretion of fat and nitrogen in the stools was determined in each patient. During the basal periods these individuals excreted in their stools from two to six times more fat than a control group of patients. Likewise, during the basal periods two individuals excreted normal amounts of nitrogen in their stools, while the third subject (A. Z.) excreted from two to three times more nitrogen than the control individuals (Table IIB).

It would appear, then, that those patients who had undergone total gastrectomy manifested a pronounced steatorrhea in all instances and a conspicuous creatorrhea in one instance. This demonstration of a disturbance in alimentary digestion and absorption presented a strong argument indicating the association of anemia with alimentary tract dysfunction.

(6) Blood loss or increased blood destruction. It has been well established that continued blood loss from the body or increased blood destruction within the body as with intravascular hemolysis will cause or aggravate an anemia.[22] In order to investigate this possibility as a cause for the anemia in the patients in the present study, frequent examinations were carried out on each patient to ascertain blood loss in the excreta and the oral cavity and increased amounts of bilirubin in the circulating blood. Hematuria, blood from the oral cavity, blood in the stools, and hyperbilirubinemia were not demonstrated in any instance.

Thus, it can be concluded that the anemia in those patients having undergone gastrectomy was not due to blood loss or increased blood destruction.

To summarize.—It seems probable that the anemia in the patients having undergone total gastrectomy was not due to a deficiency of dietary protein, intrinsic or extrinsic factors, or to the presence of an infection. However, there may have been a relationship between the anemia and a disturbance in alimentary digestion and/or absorption and, in one instance, to a disturbance in the bone marrow function.

DISCUSSION

It has been demonstrated in this investigation that patients who have undergone total gastrectomy for carcinoma of the stomach manifest a steatorrhea and an anemia and, in one instance, a creatorrhea, despite a survival period which would be expected to be adequate and allow for physiologic adaptation to the altered alimentary tract as the result of resection of the stomach. These experiments have demonstrated that the steatorrhea and creatorrhea were of dietary origin. The finding of an interrelationship between dietary protein and fecal nitrogen is in contrast to the observations of Coffey, Mann, and Bollmann,[12] who believed that excess nitrogen elimination in the stools was related to the bulk of the stools and not to the dietary nitrogen.

From the results of the experiments presented it appears that the steatorrhea may have been due to a pancreatic enzyme insufficiency and a dietary protein deficiency. The evidence for such a conclusion was that (1) the administration of pancreatic enzymes and (2) the administration of large amounts of dietary protein was followed by a decrease in the steatorrhea. The explanation for a pancreatic insufficiency was not clear since organic disease of the pancreas was not demonstrated in any patient at the time of operation nor suspected from the clinical course or history. Furthermore, repeated experimental and clinical observations have indicated that as long as small amounts of exocrine function of the pancreas persist the intestinal digestion dependent upon pancreatic enzymes will be carried out in a normal fashion.[23]

A "primary" or macrocytic anemia was not demonstrated in any of the patients studied. The follow-up period in no case exceeded twenty months, so it is possible that sufficient time had not elapsed for a "primary" anemia to develop as the result of the absence of a stomach.

The anemias demonstrated in this study were of the normochromic, normocytic type and refractory to the administration of increased dietary protein, intrinsic and extrinsic factors. The anemia may be dependent upon defective or deficient nutrition. Such a nutritional deficiency state may arise from an inability to utilize and distribute the necessary substances from the diet as well as from a dietary deficiency or defect itself. It has been our clinical experience that patients with cancer of the gastrointestinal tract frequently manifest a mild or moderate anemia, despite a seemingly adequate diet, that is refractory to the usual forms of therapy, i.e., iron compounds, high protein diet, and liver extract. Macrocytosis has been frequently demonstrated in patients with cancer of the gastrointestinal tract, however.[6] The present study has indicated the inability of these patients to utilize properly the dietary fat and, in one instance, the dietary protein. Other studies from this hospital have indicated that patients with cancer of the gastrointestinal tract have difficulty in utilizing such substances as vitamin A and vitamin K.[6, 7]

CONCLUSION

Patients who have had total gastrectomy for carcinoma of the stomach have an impaired ability either to digest or absorb the fat of the diet and, in one patient, the protein of the diet.

A deficiency of bile salts or a pancreatic hormone, lipocaic, could not be considered causative factors for the disturbed lipid metabolism.

Pancreatic enzyme appeared to be effective in reducing the steatorrhea in the one patient studied.

Beef supplements to the diet were effective in reducing the steatorrhea in two of the three patients studied.

A refractory rather than a macrocytic anemia was demonstrated.

CASE REPORTS

PATIENT A. Z. (total gastrectomy for carcinoma of the stomach).—A. Z., a 59-year-old man, was admitted to the hospital August, 1940, complaining of alternating bouts of diarrhea and constipation associated with mild postprandial, substernal, and epigastric pain. Roentgenographic studies showed an irregular polypoid lesion in the upper portion of the stomach and rigidity along the lesser curvature.

Total gastrectomy was performed with an end-to-side anastomosis between the end of the esophagus and loop of jejunum and a side-to-side jejunojejunostomy. A Marwedel type of jejunostomy was established for temporary feeding purposes.

From September, 1940, to August, 1941, the patient was able to eat three regular meals each day with only occasional distress. There was a five to eight pound weight gain in three months. There was no diarrhea. No specific vitamin or enzyme therapy was given during this period.

In August, 1941, the patient was readmitted to the hospital for metabolic studies. He was given a basal diet which consisted of carbohydrate 380 Gm., protein from 60 to 70 Gm., and fat 40 Gm. No metabolic studies were performed for a period of seven days in order to allow the patient to become adjusted to the diet and hospital routine. The present investigation was then begun.

These investigations were performed:

Basal diet	8 periods
Fat free diet	4 periods
Basal diet + 70 Gm. gelatin daily	3 periods
Basal diet + 100 Gm. beef protein daily	7 periods
Basal diet + 6 Gm. lipocaic daily	3 periods
Basal diet + 12 Gm. pancreatic enzymes daily	1 period
Basal diet + 25 Gm. pancreatic enzymes daily	2 periods
Basal diet + 4 Gm. bile salts daily	1 period
Basal diet + 180 Gm. fat	1 period
Basal diet + 50 Gm. ventriculin daily	3 periods
Basal diet + 5 ml. crude liver extract daily	4 periods

Periods of basal diet feedings were placed between each of these tests. Periods were of three to four days each in all instances except one.

Large feedings occasionally caused some epigastric distress which could be relieved by smaller and more frequent feedings. Otherwise the metabolic studies were tolerated well and the patient was finally discharged to the outpatient clinic for follow-up studies. His weight, blood, and physical picture have remained unchanged.

Pathologic Study.—The specimen was a totally excised stomach measuring 40 cm. along the greater curvature and 16 cm. along the lesser curvature. Portions of the great and gastrohepatic omenta were attached to the stomach. There was no evidence of lymph nodes involved with carcinoma along the greater curvature. In the region of the lesser curvature there was a great deal of induration and definite evidence of infiltration by tumor in the fat. The lymph nodes in this region were quite soft. Tumor was seen in a diffuse and shotty distribution just beneath the serosa on the anterior and posterior surfaces bordering on the lesser curvature. On opening the stomach there was a very bulky, widely ulcerated carcinoma, the edges of which were firm and elevated to a height of nearly 1 cm. The tumor extended for a distance of 11 cm. along the lesser curvature and 3 cm. down the anterior and posterior walls. The proximal edge was approximately 3 cm. from the line of amputation. The gastric mucosa was covered by a copious layer of mucinous material. The usual gastric rugae markings were largely obliterated except for about 5 cm. of the prepyloric area.

Microscopic Study.—Adenocarcinoma, grade 4, with fat invasion at the lesser curvature, was found; no definite nodal metastases. Mucosal atrophy was marked. Intestinal metaplasia was present.

Laboratory Data.—At time of metabolic studies laboratory data revealed urine normal, except for an occasional faint trace of albumin; urinary glucuronates, 800 mg. per twenty-four hours. Stools were yellow-brown, soft, bulky, and somewhat foul. Guaiac test for blood was negative on repeated examinations and negative for sugar after acid hydrolysis. Blood chemistry was: bilirubin, 1.0 mg. per cent; cholesterol, total, 164 mg. per cent, free, 49 mg. per cent, esters, 115 mg. per cent; prothrombin, 92 mg. per cent; alkaline phosphatase, 4.9 units; calcium, 11.9 mg. per cent; phosphorus, 4.33 mg. per cent; plasma vitamin A, 175 U.S.P. units; and carotene plasma, 0.08 U.S.P. units.

Glucose tolerance test, after ingestion of 100 Gm. of glucose, showed:

Time (minutes)	Fasting	30	60	120	180
First test					
Glucose in blood (mg. per cent)	83	200	238	70	61
Second test	76	213	170	64	63

A preoperative gastric analysis showed:

	Free Acid (N/10 HCl)	Combined Acid (N/10 HCl)
Before histamine	0 ml.	36 ml.
15 min. after histamine	0 ml.	36 ml.
30 min. after histamine	0 ml.	46 ml.
60 min. after histamine	0 ml.	18 ml.

The first specimen was positive for blood; all subsequent specimens were negative for blood and bile.

The sternal marrow was found to be normal bone marrow.

PATIENT J. C. (total gastrectomy for carcinoma of the stomach).—J. C., a man, aged 55 years, was admitted to the hospital March, 1940, complaining of postprandial distress and gaseous eructation not relieved by soda or food. Roentgenographic studies showed a circular defect in the mid-portion of the antrum of the stomach and a loss of rugal pattern throughout the pars media.

A total gastrectomy was performed with an end-to-side anastomosis between the end of the esophagus and loop of jejunum and a side-to-side jejunojejunostomy. A Marwedel type of jejunostomy was established for temporary feeding purposes. The patient was discharged on his thirty-ninth postoperative day on a liquid diet supplemented with purées and gruels. Follow-up studies were carried out in the outpatient department during the next three months when it was noted that the patient ate fairly well but experienced some distress after eating large meals. He continued to lose weight slowly.

The patient was rehospitalized in July, 1940, for metabolic studies. He was placed on a basal analyzed diet made up from foodstuffs from a regular hospital menu and containing 300 Gm. of carbohydrate, 70 to 80 Gm. of fat and 80 Gm. of protein. After a period of seven days for adjustment to the diet and hospital routine the following studies were performed:

Basal diet	2 periods
Basal diet + 50 Gm. of fat	2 periods
Basal diet + 70 Gm. of beef protein	2 periods
Basal diet + oral liver extract	1 period

Periods of basal diet feeding were placed between the fat and beef supplement periods.

The metabolic studies were tolerated well. Frequent small feedings caused less epigastric distress and a slight gain in weight.

The patient was followed in the outpatient department, where studies with yeast and bile salts, supplements to the diet, were attempted, but proper evaluation of these agents could not be carried out due to dietary indiscretions and lack of cooperation on the part of the patient.

The patient died at home in October, 1941. Necropsy was not performed.

Pathologic Study.—The stomach was involved by an extensive scirrhous type of cancer with serosal infiltration but without visible or palpable metastases to nodes or adjacent mesothelial surfaces. The growth extended to within 1 cm. of the esophagus on the lesser curvature. The specimen appeared to be a total gastrectomy with a small portion of the duodenum. A large tumor measuring 8 by 4.5 by 2.5 cm. extended along the lesser curvature 8 cm. distant from the duodenal line of excision to 2 cm. distance from the esophageal line of excision. The mucosa over the tumor was flat, had lost its rugae, and was paler than the surrounding mucosa. There were three ulcerated areas over the tumor proper. Three and one-half centimeters from the duodenal incision was a soft sessile polyp 2 cm. in diameter. The remaining gastric mucosa was moderately infected.

Microscopic Study.—Examination showed adenocarcinoma, grade 3 or 4, perforating to the serosal surface. The polyp was adenomatous only. No nodes were found.

Laboratory Data.—At postoperative study, urine showed an occasional slight trace of albumin, with normal sediment and urinary gluconates, 460 mg. per twenty-four-hour period; a Fishberg concentration test carried out July 31, 1941, showed a maximum specific gravity of 1.014. Stools were brown, well formed, and of the usual consistency. Guaiac test for blood was negative. Blood chemistry showed urea nitrogen, 11.1 mg. per cent; bilirubin, 0.5 mg. per cent; cholesterol, total, 147 mg. per cent; cholesterol, free, 66 mg. per cent; cholesterol esters, 81 mg. per cent; prothrombin, 96 mg. per cent; calcium, 10.8 mg. per cent; phosphorus, 4.3 mg. per cent; plasma vitamin A, 130 U.S.P. units; carotene (plasma), 0.10 U.S.P. units; thiamine, red blood cells, 10 micrograms per 100 ml.; and leucocytes, 101 micrograms per 100 ml.; Kahn and Kline serologic tests were negative.

Glucose tolerance test, after ingestion of 100 Gm. of glucose, revealed:

Time (minutes)	Fasting	30	60	120	180
Glucose in blood, mg. per cent	101.5	129.2	247	120.5	60.4

No glycosuria

A preoperative gastric analysis showed:

	Free Acid (N/10 HCl)	Combined Acid (N/10 HCl)
Before histamine	0 ml.	8 ml.
15 min. after histamine	0 ml.	10 ml.
30 min. after histamine	0 ml.	10 ml.
45 min. after histamine	0 ml.	8 ml.
60 min. after histamine	0 ml.	8 ml.

There was insufficient postoperative material for analysis.

PATIENT D. S. (total gastrectomy for carcinoma of stomach).—D. S., a 42-year-old woman, was admitted to the hospital in January, 1940, for metabolic studies. Total gastrectomy for a linitis plastica type of carcinoma of the stomach had been performed at another hospital in November, 1938. An end-to-side esophagojejunostomy and side-to-side jejunojejunostomy were established as well as a jejunostomy for temporary feeding purposes. In the twelve months' interval between hospitalizations there was a weight loss of thirty pounds despite a fair appetite and the consumption of a fairly adequate diet.

On admission to the hospital, in January, 1940, the patient was given a basal diet made up from regular hospital foodstuffs which consisted of 30 to 35 Gm. of protein, 60 Gm. of fat, and 450 Gm. of carbohydrate. No metabolic studies were performed for a period of six days in order to allow the patient to become adjusted to the diet and new environment.

The following studies were then carried out:

Basal diet	2 periods
Basal diet + 50 Gm. of fat daily	2 periods
Basal diet + 80 Gm. beef protein daily	2 periods

Basal period feedings were inserted between the fat and beef supplement periods.

It was found desirable to feed the patient six feedings a day to relieve a slight postprandial epigastric distress. Otherwise the metabolic studies proceeded in a smooth fashion.

The patient was discharged to her home and care of her family physician.

In October, 1940, multiple and diffuse carcinoma metastases were demonstrated in the peripheral lymph nodes, the operative wound, and bony skeleton. Death occurred in November, 1940. Necropsy was not performed.

Laboratory Data.—At postoperative examination at Memorial Hospital, urine was normal and urinary glucuronates 400 mg. per twenty-four hours. Stools were brown, well formed, and of usual consistency. Guaiac test for blood was negative. Blood chemistry showed urea nitrogen, 7.4 mg. per cent; bilirubin, 0.25 mg. per cent; serum protein, 6.0 mg. per cent; serum sodium chloride, 700 mg. per cent; total cholesterol, 91.2 mg. per cent; free cholesterol, 47.6 mg. per cent; cholesterol esters, 43.6 mg. per cent; bilirubin, 0.5 mg. per cent; prothrombin, 78 mg. per cent; plasma vitamin A, 126 U.S.P. units; and carotene plasma, 0.08 U.S.P. units.

Glucose tolerance test, after ingestion of 100 Gm. of glucose, revealed:

Time (minutes)	Fasting	30	60	120	180
Glucose in blood, mg. per cent	73.5	140.8	157.4	132	56

No glycosuria

Pathologic Study of Stomach (November 9, 1938):

Gross: The specimen was a small contracted stomach with firm, cartilage-like thickening of the wall of the upper half encircling it and extending into the fundus. There was diffuse thickening and edema of the entire stomach wall. The wall measured 1 cm. in thickness. The stomach measured 22.0 cm. in length and 7 cm. in its greatest diameter. No abnormal lymph nodes were encountered. The mucosa was flattened and rugae were absent. There was no ulceration.

Microscopic: The character of the fibrosis was that of linitis plastica. There was a chronic gastritis. Clusters of cells were seen in the desmoplastic submucosa, which were diagnosed as cancer.

Laboratory Data: Study revealed urine normal. The stools were small, brown, and well formed, and blood was demonstrated preoperatively but not postoperatively.

Blood chemistry:

	Oct. 5, 1940	Oct. 25, 1940
Urea nitrogen	17.6 mg. per cent	19.6 mg. per cent
Bilirubin	0.6 mg. per cent	
Calcium	9.8 mg. per cent	11.5 mg. per cent
Phosphorus	4.6 mg. per cent	
Phosphatase		6.4 units
Serum albumin		3.9 mg. per cent
Serum globulin		1.9 mg. per cent

Glucose tolerance test, after ingestion of 70 Gm. of glucose, showed:

Time (minutes)	Fasting	30	60	120	180
Glucose in blood, mg. per cent	115	280	260	153	114
Glucose in urine	0	1.4	0	0	0

The basal metabolic rate was −8 per cent and −11 per cent.

A preoperative gastric analysis showed:

	Free Acid (N/10 HCl)	Combined Acid (N/10 HCl)
Before histamine	8 ml.	20 ml.
5 min. after histamine	14 ml.	24 ml.
15 min. after histamine	18 ml.	28 ml.
30 min. after histamine	12 ml.	22 ml.
60 min. after histamine	10 ml.	20 ml.

REFERENCES

1. Gordon-Taylor, G., Hudson, R. V., Dodds, E. C., Warner, J. L., and Whitby, L. E. H.: The Remote Results of Gastrectomy, Brit. J. Surg. **16**: 641-667, 1929.
2. Wróblewski, A.: Eine chemische Notiz zur Schlatter'schen totalen Magenexstirpation, Centralbl. f. Physiol. **11**: 665-668, 1897.
3. Schlatter, C.: Ueber Ernährung und Verdauung nach völlständiger Entfernung des Magens. Oesophagoenterostomie beim Menschen, Beitr. z. klin. Chir. **19**: 757-776, 1897.
4. Lublin, H.: On Late Symptoms After Gastroenterostomy and Resection of Stomach (Billroth II) for Gastric and Duodenal Ulcer, Acta med. Scandinav. supp. 41, 1-131, 1931.
5. Rekers, P. E., Abels, J. C., and Rhoads, C. P.: Metabolic Studies in Patients With Cancer of the Gastrointestinal Tract. IV. Fat Metabolism—a Method of Study, J. Clin. Investigation **22**: 243-248, 1943.
6. Abels, J. C., Rekers, P. E., Binkley, G. E., Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients With Cancer of the Gastrointestinal Tract. II. Hepatic Dysfunction, Ann. Int. Med. **16**: 221-240, 1942.
7. Abels, J. C., Gorham, A. T., Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients With Cancer of the Gastrointestinal Tract. I. Plasma Vitamin A Levels in Patients With Malignant Neoplastic Disease, Particularly of the Gastrointestinal Tract, J. Clin. Investigation **20**: 749-764, 1941.
8. a. Thaysen, T. E. H.: Non-Tropical Sprue, a Study in Idiopathic Steatorrhea, Copenhagen, 1932, Levin & Munksgaard.
   b. Thaysen, T. E. H.: Ten Cases of Idiopathic Steatorrhea, Quart. J. Med. **4**: 359-395, 1935.
9. Bassett, S. H., Keutmann, E. H., Hyde, H. V., and Van Alstine, H. E.: Metabolism in Idiopathic Steatorrhea. I. Influence of Dietary and Other Factors on Lipid and Mineral Balance, J. Clin. Investigation **18**: 101-120, 1939.
10. Dragstedt, L.: The Present Status of Lipocaic, J. A. M. A. **114**: 29-32, 1940.
11. Beazell, J. M., Schmidt, C. R., and Ivy, A. C.: On Effectiveness of Orally Administered Diastase in Achylia Pancreatica, J. Nutrition **13**: 29-37, 1937.
12. Coffey, R. J., Mann, F. C., and Bollmann, J. L.: III. The Influence of the Pancreas on the Utilization of Foodstuffs, Am. J. Digest. Dis. **7**: 144-149, 1940.
13. Rekers, P. E., Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients With Cancer of the Gastrointestinal Tract. V. Pancreatic Insufficiency in a Patient Treated Surgically for Carcinoma of the Ampulla of Vater, J. A. M. A. (In press.)
14. Munk and Rosenheim: Quoted by Magnus-Levy, Adolf: The Physiology of Metabolism, in: von Noorden, Carl: Metabolism and Practical Medicine, Chicago, 1907, W. T. Keener & Co., vol. I, p. 442.
15. Barker, W. H., and Hummel, L. E.: Macrocytic Anemia in Association With Intestinal Strictures and Anastomoses, Bull. Johns Hopkins Hosp. **64**: 215-256, 1939.

16. Castle, W. B., Rhoads, C. P., Lawson, H. A., and Payne, G. C.: Etiology and Treatment of Sprue, Arch. Int. Med. **56**: 627-699, 1935.
17. Meulengracht, E.: Etiological Factors in Pernicious Anemia. Univ. Wisconsin, Symposium on Blood, Madison, 1939, pp. 72-82.
18. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia. Study of 105 Cases, J. A. M. A. **89**: 759-766, 1927.
19. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. I. The Effect of Administration to Patients With Pernicious Anemia of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, Am. J. Med. Sc. **178**: 748-764, 1929.
20. Whipple, G. H.: Hemoglobin and the Plasma Proteins: Their Production, Utilization and Inter-relation, Am. J. Med. Sc. **203**: 477-489, 1942.
21. Rhoads, C. P.: Aplastic Anemia. Univ. Wisconsin, Symposium on Blood, Madison, 1939, pp. 31-40.
22. Haden, R. L.: The Nature of Hemolytic Anemia, Univ. Wisconsin, Symposium on Blood, Madison, 1939, pp. 83-104.
23. Graham, E. A., and Hartmann, A. F.: Subtotal Resection of the Pancreas for Hypoglycemia, Surg., Gynec. & Obst. **59**: 474-479, 1934.

UNILATERAL DECAPSULATION OF KIDNEY FOR TRANSFUSION OLIGURIA

SPENCER C. FLO, M.D., AND HARWOOD W. CUMMINGS, M.D.
GREENFIELD, MASS.

DECAPSULATION of the kidney has been so discredited in the past that the medical profession has accepted it somewhat reluctantly as a lifesaving measure in cases of transfusion oliguria. Very little has been written in recent years on this subject, but Nichol[1] has reviewed the theories covering the mechanism of decapsulation and we are quoting liberally from his article. The operation was first performed by Reginald Harrison of England,[1] in 1878. Later Rovsing and Edebohls did a similar operation for Bright's disease. Many hundreds of such cases so treated were reported at that time, but the classification was so confused and the results so equivocal, that the procedure was condemned.

The anatomy of the renal capsule has been clearly described by Rolnik[1] of Chicago:

> The renal capsule, the true or fibrous capsule, is a fibromuscular structure which contains some smooth muscle and elastic fibers. It envelops the kidney somewhat loosely, but quite securely, and covers it much in the manner of a hood, being firmly attached at its neck or hilus where the pelvis and vessels enter, and covering its surface rather loosely. Due to this arrangement the capsule can be readily freed from the surface of the kidney, and thus decapsulation can be done without injury to the parenchyma. All other parenchymatous organs have a capsule which is firmly attached and which cannot be removed, except by tearing of the surface, and often producing considerable trauma. The elastic fibro-muscular structure of the capsule, together with its rather loose attachment to the surface of the kidney, permits it to accommodate itself readily to any rapid variation in the size of the kidney, which may occur as result of change in intrarenal tension.

The following theories have been advanced to show why decapsulations are of value for nephritis:

1. Harrison stated that decapsulation simply relieves tension in the kidney.

2. Volhard thought the mechanical effect of handling and squeezing the kidney at operation probably caused a protein shock.

3. Horder[5] compared the operation with a simple wet cupping, i.e., oozing from the denuded cortex.

4. R. K. Sen of Vienna suggested that the opening of lymphatic channels from the cortex is the important factor, and through these chan-

Received for publication, Dec. 31, 1942.

nels it is possible to drain an infected renal cortex. In support of this theory he drew attention to the fact that there is frequently a profuse flow of clear discharge from the draining tract leading to the kidney cortex.

5. Many believe the good effects of decapsulation for nephritis are brought about by a profuse collateral circulation developed immediately following operation. This has been definitely disproved by Haslinger and Rolnick,[1] who have shown that the new capsule is thicker than the original, but the benefits of the operation long outlast the short period required to develop a new capsule. It has been found by experimenters that within a period of seven to ten days after decapsulation, a newly formed capsule is on its way to development and is well established within three weeks. This continues to increase in thickness for two months. The new capsule which replaces the old is not similar to the original, for it consists of scar tissue only. It has no elasticity, is firmly adherent to the kidney surface, and infiltrates the cortex. While some European surgeons speak of repeated decapsulations, it is not possible to separate this new capsule without tearing the renal parenchyma. There is no space between the cortex and the new capsule allowing for free interchange of fluid and lymph. It has been demonstrated that indigo carmine injected under one normal capsule is rapidly excreted from both kidneys, so there must be a free interchange between the renal parenchyma and this fluid.

6. Fisher did much work on anastomosis of sympathetic nerves of the kidney capsule. In general, these nerves run independently of the vessel nerves in the kidney parenchyma adjacent to the capsule. A network of all the capsular nerves lies at the hilus, and Fisher is of the opinion that this in some reflex manner influences the flow of blood through the kidney. He claims that faradic and mechanical stimulation of the capsule decreases the volume of the kidney without any appreciable effect on the blood pressure. He concludes that the renal capsule is a reflex-regulating apparatus for blood flow through the kidney. Decapsulation breaks up the sympathetic connections between the cortex and the capsule, and thus in reality is a sympathectomy. In inflammation of the kidney spasms of blood vessels play a major part and in decapsulation the breaking up of the sympathetic system causes the vessels to lose their vasomotor tone. Accordingly, by decapsulation, the blood circulation of the kidney is improved and the damage caused by stagnant toxins is eliminated, as these toxins are harmful to the secretory and excretory systems of the kidney.

Regardless of the mechanism involved in decapsulation, when used for transfusion oliguria, where bilateral operation was done, the results have been spectacularly good. Of course, it will always be debated whether or not the beneficial effect is purely coincidental. A great deal of experimental work could still be done in this field. Notwithstanding

the immediate benefits, there is little question that the kidneys remain permanently damaged, because of the denseness and adherence of the newly formed capsules. Ravich,[2] for example, refers to cases which have had bilateral decapsulation, where subsequent intercurrent infections caused fresh embarrassment of the kidneys, and ended in death because further decapsulation could not be performed.

Very few cases of unilateral decapsulation have been reported, but Forbes and Packard[3] did a unilateral decapsulation for nephritis, following an appendectomy, with diuresis and recovery, although they failed to describe the condition of the kidneys postoperatively. Ravich[2] described a case of unilateral decapsulation for transfusion oliguria with diuresis and recovery, but he too, failed to show the postoperative state of the kidneys, except to say that they functioned normally. If it is true that both kidneys will respond to unilateral decapsulation, then we feel that it is the procedure of choice, because if anything should happen to the decapsulated kidney, there would still be a definite margin of safety, an intact kidney.

REPORT OF A CASE

A 48-year-old woman who had always enjoyed good health had been transfused seven days prior to her admission to this hospital. The day before her transfusion she had had a diagnostic curettage and amputation of the cervix because of vaginal bleeding of twelve days' duration. The preoperative blood studies showed a red count of 3,550,000 and a hemoglobin of 71 per cent, but because the patient had felt "washed out" and tired, her local doctor thought the giving of some blood would hasten her recovery. After 450 c.c. of citrated blood had been injected, it was noted that she was in severe shock. She rapidly responded to the usual supportive treatment, but upon catheterization twelve hours later, 200 c.c. of black urine were obtained. At this time we saw the patient in consultation. Nausea and vomiting had begun shortly after transfusion, necessitating Wangensteen drainage. It was estimated that her stomach drainage was 1,000 to 1,200 c.c. daily and insensible fluid loss 1,000 c.c. She was given 3,000 c.c. of intravenous fluids daily, consisting of 1,000 c.c. 5 per cent glucose in physiologic saline solution, and 2,000 c.c. 5 per cent glucose in distilled water. Her local doctor attempted to combat acidosis by soda bicarbonate orally but this was ineffectual because of vomiting.

During the next week her urinary output was 60 to 90 cc. for each twenty-four-hour period. The urine was very concentrated, showing 4 plus albumin, slight acetone, and many white blood cells. During the latter part of the week she began to have edema of the face and extremities and became very drowsy. Her blood pressure had risen from 120/60 to 140/80. At this time it was thought wise to transfer her to the Franklin County Public Hospital.

Our examination revealed a woman with generalized edema. The lungs were clear and the abdomen slightly distended, possibly due to edema of the overlying subcutaneous tissues. Both kidneys were markedly enlarged and tender. The heart was normal and the blood pressure 140/70. Pelvic examination was not done, but she had very little vaginal bleeding since operation. The blood chlorides were 490 mg. The red blood count was 1,775,000, hemoglobin 35 per cent, white blood count 8,700, polymorphonuclears 86 per cent, and the blood nonprotein nitrogen 118 mg.

The following day the urinary output was about the same and general condition had not changed. The next day, nine days after transfusion, she seemed more

stuporous. The nonprotein nitrogen had risen to 180 mg. On this day her hemoglobin was 28 per cent, red blood count 1,920,000, white blood count 16,300, with 94 per cent polymorphonuclear cells. A unilateral decapsulation was elected because of severe secondary anemia and poor general condition.

The left kidney was operated upon under local anesthesia, a subcostal incision was made and great care was taken throughout the operation to ligate vessels as we went along, using No. 50 cotton. The kidney was markedly enlarged, purplish blue, and bulged through the incised capsule, with some escape of fluid. It was stripped to the hilus. There were no remaining areas of constriction, and no apparent injury to the parenchyma during the procedure. A drain was placed in the depth of the wound and the incision closed in layers, using No. 30 cotton. The patient's condition at the end of the operation was no worse than before.

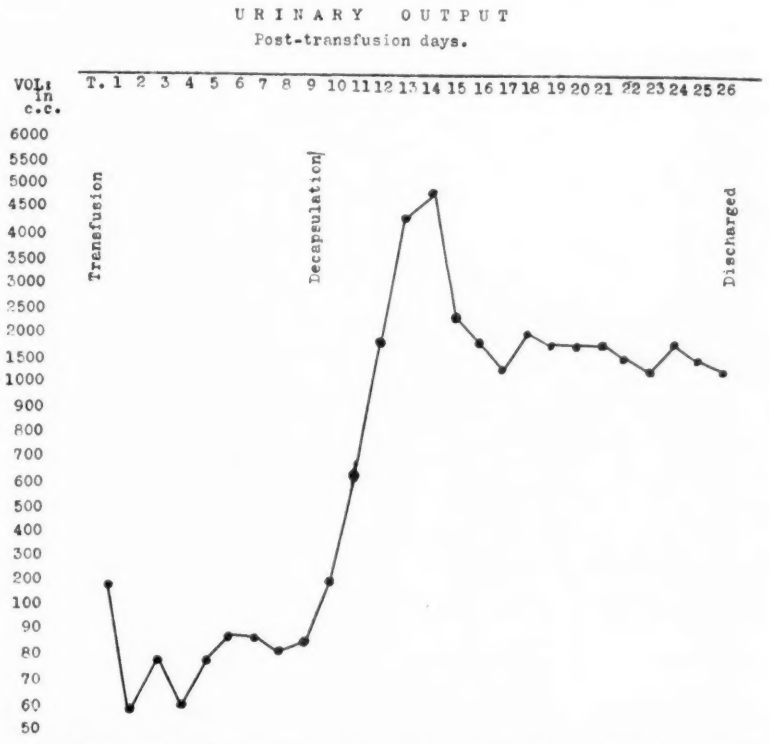


Fig. 1.—Intake of fluids, from two days after transfusion until two days after decapsulation, was consistently 3000 c.c. intravenous (2000 c.c. of 5 per cent glucose in distilled water, and 1000 c.c. of 5 per cent glucose in normal saline solution).

Immediately after surgery she seemed better; vomiting ceased, she was more alert, and her spirits improved. The intravenous fluids were continued as before, as well as large doses of cevitamic acid. Plasma or any other proteins were not given for replacement, because we were fearful of what any foreign protein might do to the already damaged kidneys. She was catheterized every twelve hours postoperatively. The first twenty-four-hour period produced 211 c.c. of urine with a foul odor, cultures of which showed colon bacillus. At this time the Wangensteen tube was clamped and she was able to take cracked ice without further vomiting. The second twenty-four-hour postoperative period produced 625 c.c. of much clearer urine. Now the nonprotein nitrogen was 215 mg., the blood pressure was 160/60, the patient was taking liquids by mouth, and intravenous therapy was discontinued. In

the third twenty-four-hour period 340 c.c. of urine were obtained by catheter, but during the night marked diuresis started, and she had large involuntary voidings. At this time there was a large amount of serous drainage from the wound. Thereafter she was able to pass much urine (Fig. 1). The edema rapidly disappeared and her kidneys were no longer palpable. As soon as tolerated, a high protein diet was given, as well as large doses of iron, but the blood and hemoglobin regenerated slowly. She continued to improve from this time on, except for marked mental confusion on the fifth postoperative day. The psychiatrist who saw her felt this condition was probably due to sudden loss of fluids, and the confusion was controlled by paraldehyde.

She was discharged on the eighteenth postoperative day. The red blood count was then 2,440,000, hemoglobin 42 per cent, white blood count 6,100, and the nonprotein nitrogen 20 mg. per cent. The wound healed by first intention. The pathologic report of the previous operation had returned and, as it showed no malignancy, she was sterilized by x-ray for functional uterine bleeding.

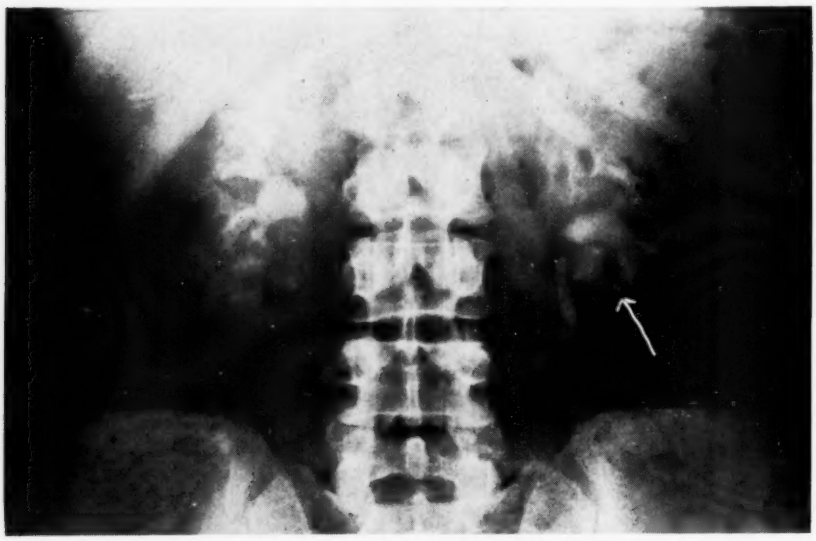


Fig. 2.—Eight minutes after injection of diodrast. (Courtesy of Dr. Felix G. Fleischner, Beth Israel Hospital, Boston.

In her home-town the patient had been typed as of Group II, by the Moss technique, and the donor as of Group IV. A recheck by us revealed the patient to be a type IV and the donor type II. The cross-matching showed rapid agglutination with hemolysis, so that within five minutes, no clumping was observed, as the clumps had been hemolyzed.

The patient was seen two months later. She was feeling very well except for multiple joint pains, although she had never had rheumatism in the past, presumably menopausal arthralgia or some joint change resulting from the transfusion reaction. Hemoglobin was 75 per cent, the red blood count 4,000,000, the nonprotein nitrogen 20 mg. Complete urologic studies were made and cystoscopic examination revealed a normal bladder; catheters were placed in each kidney pelvis, and there was a clear, intermittent drip bilaterally. A split function showed appearance of dye on the right in 3 minutes, and on the left in 3½ minutes. Intravenous pyelograms were carried out and the results can be seen by the following photographs, with a report by the roentgenologist. Fleischner of Boston says:

The left kidney is slightly lower than normal. Intravenous pyelography, performed with diodrast, showed good excretion of dye on either side after eight minutes. On the eight minute film, groups of pinhead sized deposits of dye were seen in the medial lower quadrant of the left kidney, otherwise the calyces and kidney pelvis were well outlined. The films taken after twenty minutes showed these small deposits communicating and emptying into the lower calyx and the pelvis. On the left there is a kink at the ureteropelvic junction and atony of the upper third of the ureter. The significant result of this examination is the fact that the left as well as the right kidney showed normal excretion and good concentration of dye with the intrarenal passages well preserved in width and shape. There was a single unusual finding; the small deposits of dye, for which observation we have been unable to find an analogy in the literature accessible to us. Thus, we feel compelled to advance a tentative interpretation of this observation. The small "cavities," as visualized by the dye, located in the cortex of the medial lower quadrant of the kidney, receive their dye from the excretory system of the kidney. There has been, apparently, minimal traumatization of this portion of the kidney parenchyma, resulting in interference with some of the collecting tubules. Small pools have been formed, and by some kind of recanalization, drainage of these pools to the calyx has been established to compensate for the supposed localized damage.

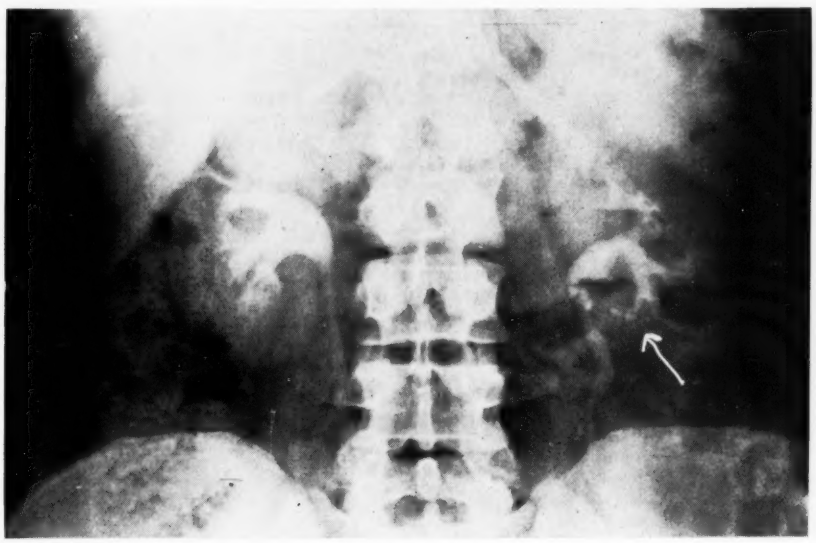


Fig. 3.—Twenty minutes after injection of diodrast. (Courtesy of Dr. Felix G. Fleischner, Beth Israel Hospital, Boston.)

It is to be understood that decapsulation is not to be employed until medical and supportive measures have failed. We feel the most important medical treatment is the intelligent use of fluids. Coller[4] states that "water balance should be maintained with isotonic glucose solution, taking into account the insensible loss and that lost by vomiting and Wangensteen drainage. Sodium chloride solution should be used only to cover salt losses by vomiting and drainage, and aside from this should never exceed more than one-half liter a day. The CO_2 combining power should be kept above 60 by use of sodium lactate solutions, 1/6 molar."

After an arbitrary period of about one week of medical and supportive treatment which has failed to increase appreciably the urinary output, decapsulation must be considered, as the patients in a few of the reported cases of late decapsulation have died, even after the onset of brisk diuresis, and autopsy has revealed severe necrosis of the kidney. We feel that no case should be allowed to terminate fatally for the patient without the benefit of surgery.

We have presented a case of uremia, following transfusion reaction, apparently cured by unilateral decapsulation of the kidney. The exact mechanism is not clearly understood and certainly deserves investigation, both clinically and experimentally. Since the patient's condition was becoming progressively worse, and spontaneous recovery was despaired of, we felt that a unilateral decapsulation would do less harm than bilateral, and that bilateral might cause enough shock to result in an unfavorable outcome. If a unilateral decapsulation will break the vicious chain of events, this is the procedure of choice, especially in view of the damage to the kidney such an operation must entail.

REFERENCES

1. Nichol, J. E.: Indications for Decapsulation of Kidney, Canad. M. A. J. **43**: 577, 1940.
2. Ravich, A.: Transfusion Reaction With Anuria and Uremia Cured by Unilateral Renal Decapsulation, M. Rec. **154**: 403, 1940.
3. Forbes, R. P., and Packard, G. B., Jr.: Treatment of Anuria by Kidney Decapsulation, Colorado Med. **29**: 74, 1932.
4. Coller, Frederick: Ann Arbor, Mich. Personal Communication.

URINARY RETENTION FOLLOWING THE COMBINED ABDOMINOPERINEAL RESECTION

FREDERICK A. COLLER, M.D., AND PETER F. EASTMAN, M.D.
ANN ARBOR, MICH.
(From the Department of Surgery, University of Michigan, Ann Arbor)

INTRODUCTION

THE incidence and cause of urinary retention following the operation of combined abdominoperineal resection for rectal neoplasm are not clearly known despite many studies of this problem, some of which have appeared in the literature of the subject.[1-3] The occurrence of this complication is probably so variable with differing surgical techniques that observations made upon this point by any individual are of limited value so that one cannot safely generalize from them. However, the nature of certain possible pathophysiologic changes in the act of micturition can be studied by accurate yet relatively simple means and such a study should furnish valuable information of both prognostic and therapeutic value.

Adequate emptying of the bladder depends, to a considerable extent, upon proper function of the detrusor mechanism[5] which receives its major motor nerve supply from sacral roots of the second, third, and fourth parasympathetics. The position of these sacral roots and the pelvic nerves of their peripheral extension in the sacral plexus has led some previous investigators[2, 3] to conclude that a marked degree of operative trauma to these structures is inevitable during removal of the rectum and that subsequent urinary retention is due, at least in part, to atony of the bladder. Therefore, a study was made at the University Hospital to determine the effect of the one-stage combined abdominoperineal resection upon the motor activity of the urinary bladder.

METHODS AND PROCEDURE

Twenty-two unselected patients undergoing one-stage combined abdominoperineal resection with spinal anesthesia (nupercaine, 15 c.c.) were studied by means of pre- and postoperative cystometrograms. The technique employed was that described by McClellan.[4] A simplified water cystometer was used for these determinations. The preoperative study was made on the morning of operation. At this time, the bladder was filled to ultimate capacity, that is until uncontrolled voiding about the catheter was noted and readings taken. The postoperative determi-

Aided by The James and Elizabeth Inglis Fund for Surgical Research.
Received for publication, Dec. 14, 1942.

TABLE I

CYSTOMETROGRAMS*

PATIENT	SEX	AGE (YR.)	NEOPLASM	LOCATION	I. V. P. (CM. H_2O)	CAPACITY (C. C.)	HOT AND COLD	REMARKS
D. H.	M	67	Adenoca. G II	Ant. wall, 1½ in. above sphincter	35	235		Small capacity bladder, multiple urethral strictures
O. H.	M	59	Adenoca. G II	Ant. wall, low	75	100	++	Small capacity bladder, chronic cystitis
E. W.	M	51	Adenoca. G III	Ant. wall, at sphincter	80	600	++	
A. B.	F	63	Adenoca. G II	Annular, midrectum	26	400	++	
O. C.	F	59	Adenoca. G II	Post wall, midrectum	11	200	++	Not ultimate capacity
D. P.	M	59	Adenoca. G II	Midrectum, annular	28	500	++	
L. S.	M	47	Adenoca. G III	Annular, low rectum	27	625	++	
L. L.	M	41	Adenoca. G II	Annular, low rectum	50	450	++	
McN. W.	M	54	Adenoca. G II	Annular, low rectum	48	450	++	
A. F.	F	50	Adenoca. G II	Annular, low rectum	54	650	++	
M. M.	F	65	Adenoca. G II	Midrectum	30	500	++	
N. L.	F	57	Adenoca. G II	Left lat. wall, midrectum	25	525	++	
A. B.	F	67	Adenoca. G II	Annular, midrectum	29	750	++	
A. A.	F	55	Adenoca. G II	Annular, rectosigmoid	50	700	++	
D. M.	M	46	Adenoca. G II	Rectosigmoid	23	150		Small capacity bladder, cause unknown
A. R.	M	82	Adenoca. G II	Low rectum, ant. wall	50	500	++	
G. H.	M	45	Adenoca. G II	Midrectum, annular	55	500	++	
S. S.	M	45	Adenoca. G II		65	350	++	Small capacity bladder, cause unknown
G. R.	M	41	Adenoca. G II	Midrectum, post. wall	9.5	600	++	Low I. V. P., normal voiding, cause unknown
B. S.	M	70	Adenoca. G II	Low rectum, ant. wall	60	275	++	
W. N.	M		Adenoca. G II	Low rectum, ant. wall	35	300	++	
F. S.	F	28	Adenoca. G II	Small polyp. just at sphin.	24	525	++	

*Showing intravesical pressure, bladder capacity, and thermal sensation for all patients. The location and nature of the rectal neoplasm are also indicated.

nations were made twenty-four to forty-eight hours following operation, 300 c.c. of fluid were introduced into the bladder, and again cystometrograms were made. This procedure was considered adequate to demonstrate normal or abnormal detrusor activity since the intravesical pressure developed in response to this fluid volume could be compared with the intravesical pressure developed in response to a similar fluid volume in the complete cystometrogram recorded before operation. Therefore, if the patient could empty his bladder completely, as determined by postvoiding catheterization performed several days after the inlying catheter had been withdrawn (on three to seven postoperative days), no further studies of bladder motor activity were made. However, if urinary retention did develop following the catheter withdrawal, further cystometrograms, with complete bladder filling, were recorded during this period of retention. Bladder thermal sensation was determined at the time of each study by the injection of 60 c.c. of first warm and then cold water. Microscopic examination of the urinary sediment was made at the time of the other observations.

OBSERVATIONS

In Table I are presented the "normal" bladder capacity and intravesical pressure at capacity for each patient. Table II presents a comparison of the intravesical pressure developed in response to a given fluid volume before operation with that developed at a similar fluid volume following operation by all patients on whom the one-stage combined resection of the rectum was performed. The patients who developed urinary retention following operation are indicated by an asterisk, and the further complete cystometrograms performed upon these patients during this period of retention are compared in Table III, with the normal preoperative findings taken from Table I.

Table IV presents for comparison data collected by similar observations on patients on whom colostomy was performed.

COMMENT

It will be noted in Table I, that "normal" bladder capacity and intravesical pressure vary considerably from patient to patient within this group. Although this could be attributed to previous or extant genitourinary disease in some, in others no such explanation could be found. This implies clearly that accurate evaluation of the effect of the resection of the rectum or of any other operation upon the bladder motor activity cannot be made from postoperative cystometrograms alone. It can be seen (Table II) that bladder motor activity was not weakened following operation and that thermal sensation was not lost. This was equally true whether or not the patient developed urinary retention (Table III). A significant increase in intravesical pressure at a given fluid volume will be observed in the postoperative recording in several cases where the complete resection was performed; however,

TABLE II

PATIENT	FLUID VOLUME (C. C.)	PREOPERATIVE		POSTOPERATIVE	
		I. V. P. (CM.)	THERM. SENSE	I. V. P. (CM.)	THERM. SENSE
D. H.	235	35	++	38	++
O. H.	100	75	++	75	++
E. W.*	150	10.5	++	13.5	++
A. B.*	250	20	++	38.0	++
O. C.	200	11.0	++	11.0	++
D. P.	150	9.0	++	8.0	++
L. S.	475	18.0	++	24.0	++
L. L.	200	10.5	++	21.5	++
McN. W.	250	15.0	++	25.0	++
A. F.	200	19.0	++	20.0	++
A. B.*	250	14	++	17.0	++
D. M.	150	9.5	++	9.5	++
A. A.	350	6.0	++	16.0	++
A. R.	250	25	++	27.0	++
S. S.*	300	60	++	60	++
G. R.	300	6.0	++	6.0	++
B. S.	300	12.0	++	16.0	++
W. N.*	300	35	++	35.0	++
N. L.	300	12.5	++	14.0	++

Intravesical pressure developed in response to a given fluid volume before and after the combined abdominoperineal resection.

Asterisk indicates patients who developed urinary retention.

TABLE III

PATIENT	PREOPERATIVE		POSTOPERATIVE		REMARKS
	CAPACITY	I. V. P.	CAPACITY	I. V. P.	
E. W.	600	80	575	80	Cath. out 5 days; acute retention relieved by cath. for 48 hours
A. B.	400	26	450	33	45 days cath. drainage; postoperative abscesses
A. B.	750	29	750	29	Partial retention; cath. daily 5 days
S. S.	350	65	350	63	Partial retention; cath. daily 3 days
W. N.	300	35	275	35	Partial retention; cath. daily 48 hours

Pre- and postoperative bladder capacity and intravesical pressure in patients who developed urinary retention following combined abdominoperineal resection.

TABLE IV

PATIENT	FLUID VOLUME (C.C.)	PREOPERATIVE		POSTOPERATIVE	
		I. V. P.	THERM. SENSE	I. V. P.	HOT AND COLD
M. M.	325	21.0	++	23.5	++
G. H.	150	45	++	53.0	++
B. S.	275	60	++	60	++

Presenting data similar to Table I for patients undergoing only sigmoid colostomy.

since this also took place in those patients who underwent only a palliative colostomy, it was probably due to causes other than traumatic irritation or disruption of the bladder nerve supply. Certainly the irritation of the lower genitourinary tract by the inlying catheter, the continuous decompression of the urinary bladder, and the pyuria which

all patients exhibited during the period of inlying catheterization afford sufficient explanation for this increase in bladder motor activity.

Although urinary retention did develop in five patients, in four it was of short duration. Two patients were unable to void upon catheter withdrawal. Two voided easily at this time but accumulated a residuum of urine over several succeeding days. In all cases daily catheterization for a short period gave complete relief and all of these individuals were voiding easily and carried no residual urine at the time of leaving the hospital. The fifth patient developed extensive abscesses of both anterior and posterior wounds and remained a bed patient for two months following operation. She required continuous inlying catheter drainage during this period but repeated cystometrograms showed no evidence of increased vesical capacity or decreased intravesical pressure at any time. At the time of her discharge from the hospital, two and one-half months following operation, she was voiding normally and carried no residual urine.

These observations, although they indicate that the bladder nerve supply was functionally intact following operation, still offer no explanation for the mild urinary retention which did take place in five of the patients studied. It is possible that edema of the lower urinary tract incident to trauma played some part in the two individuals who experienced acute retention when the catheter was withdrawn, since daily catheterization for a short period gave them complete relief. It is also possible that operative transection of the vesicosacral ligaments may have caused alteration in the anatomic relations between the vesical neck and membranous urethra producing mechanical obstruction to proper urine outflow. The importance of this relationship in normal voiding has been stressed by Rose in his discussion of the physiology of micturition.[6] Further study of this aspect of the problem by pre- and postoperative urethrocystogram (x-rays) is necessary to elucidate this point. In addition, urinary retention may and does occur in the absence of demonstrable bladder nerve disease or obstructive uropathy as after herniorrhaphy, hemorrhoidectomy or any laparotomy. This type of urinary retention has never been adequately explained and it is probable that such explanation will not be forthcoming until the physiology of normal voiding is better understood.

The microscopic examination of the urinary sediment indicated that all patients had pyuria and bacteriuria twenty-four to forty-eight hours after the inlying catheter had been inserted. In only one patient did any clinical evidence of lower tract infection develop. One man developed bilateral epididymitis on the tenth postoperative day, which responded within six days to orally administered sulfadiazine (3 Gm. daily) and local heat with scrotal support. The pyuria and bacteriuria had subsided prior to the discharge of the patients from the hospital. All patients were given sulfadiazine, 1.5 Gm. daily, during the period that

the catheter was inlying and for twenty-four to forty-eight hours following its withdrawal.

SUMMARY

Bladder motor activity and thermal sensation were studied in twenty-two unselected cases before and after operation for rectal cancer:

1. Preoperative cystometrograms in this series indicate a great variation in bladder capacity and intravesical pressure in subjects who have normal bladder function.

2. A comparison of pre- and postoperative cystometrograms disclosed no evidence of injury of nerves governing vesical function.

3. The etiology of the temporary urinary retention which did develop in five patients is not known; certain possible causative factors are mentioned and methods for their further elucidation are suggested.

4. Oral administration of sulfadiazine, 1.5 Gm. daily, did not prevent the development of pyuria and bacteriuria in all patients after forty-eight hours of inlying catheter drainage.

5. Abdominoperineal resection of the rectum destroys neither the autonomic nor the somatic nerve supply to the bladder.

In view of these facts it is probable that postoperative urinary retention after this operation as after some other operations, such as hemorrhoidectomy, is due to local trauma and reflex inhibition.

REFERENCES

1. Whipple, Allan O.: Complications Associated With Major Proctectomy, Ann. Surg. **96**: 916, 1932.
2. Hill, M. R., Barnes, R. W., and Courville, C. B.: Vesical Dysfunction Following Combined Abdominoperineal Resection, J. A. M. A. **109**: 1184, 1188, 1937.
3. Mullen, T. F., and Lestrohon, P.: Urologic Complications of Cancer of the Rectum, Ann. Surg. **1**: 6, 18, 1942.
4. McClellan, F. C.: The Neurogenic Bladder, Baltimore, 1939, Charles C Thomas, Publisher.
5. Langworthy, O. R., Kolb, L. C., and Lewis, L. G.: Physiology of Micturition, Baltimore, 1940, Williams & Wilkins Company.
6. Rose, D. K.: Physiology of the Bladder, J. Urol. **1**: 190, 198, 1940.

TISSUE REACTIONS TO MEDICAMENTS USED IN THE LOCAL TREATMENT OF BURNS

MARK E. MAUN, M.D., RICHARD C. SCHNEIDER, M.D.,
MATTHEW A. PILLING, M.D., AND JOHN WINSLOW HIRSHFELD, M.D.
DETROIT, MICH.

(From the Department of Pathology and the Department of Surgery, Wayne University College of Medicine, and the Surgical Service of Receiving Hospital, Detroit)

MANY surgeons have compared a burn to an open wound and have advocated treating it as such. This comparison is an apt one, since in both the continuity of the surface epithelium has been destroyed. If we accept the dictum that a burn must be regarded as an open wound, then no material should be applied to its surface which will produce further tissue damage or, in effect, make the burn more severe. Our purpose in this communication is to call attention to the tissue alterations produced on the fresh wounds of dogs by materials commonly used in the treatment of burns.

We had had the opportunity of observing the behavior of burned surfaces in seventy-five human patients treated by the application of agents commonly recommended for the local treatment of burns.[1] Many of the patients had been burned in several areas; thus each area could be treated with a different agent, and we were able to compare a large number of agents. Our observations led us to suspect that some of the eschar-forming agents increased the tissue damage, since the healing time of burns treated with these drugs was slower than that of apparently comparable burns treated with an inert ointment beneath a voluminous pressure dressing. Clinical observations of this sort are necessarily open to question, for it is difficult to estimate the depth of burns when they are first seen. In order to determine definitely whether or not our clinical impression was correct, we compared by means of biopsies the effects of tannic acid and silver nitrate and of quebracho tannin with those of vaseline gauze on human donor sites from which split-thickness grafts had been removed with the Padgett dermatome. Except for the covering of burned tissue such surfaces simulate second degree burns. This study demonstrated the destructive power of tannic acid plus silver nitrate and of quebracho tannin on human tissues in such a striking fashion that we were led to speculate about the action of other eschar-forming substances commonly employed for the local treatment of burns. Since the number of patients requiring skin grafts is limited, we were forced to resort to experimental animals.

Received for publication, March 10, 1943.

METHODS AND MATERIALS

By means of a Padgett dermatome it is possible to obtain skin injuries of almost constant depth. This machine, devised for the purpose of cutting Thiersch and split-thickness grafts, enables one to remove a uniform layer of skin of desired thickness. The knife usually removes the epidermis plus a small portion of the papillary layer of the corium. The hair follicles and the sebaceous glands in the remaining corium are left unharmed. These structures serve as a source of cells which will re-epithelize the surface of the naked dermis. The lesion produced (Fig. 1), except for the presence of a layer of burned epidermis, simulates a second degree burn. If the eschar-forming materials are capable of destroying normal tissues, their action should be manifest upon their application to such a surface.

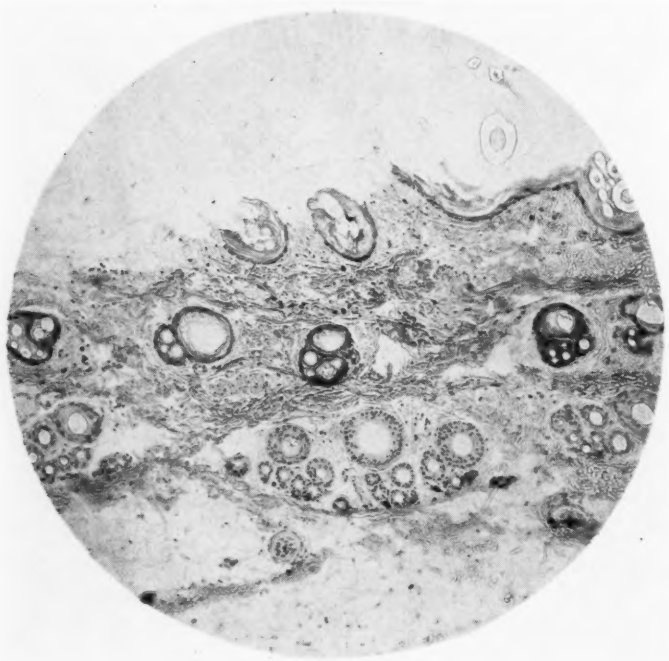


Fig. 1.—Control; donor site immediately after preparation (magnification ×100).

Eighteen dogs were anesthetized with nembutal, their hair was clipped, and their flanks and thorax were shaved; their skin was then washed thoroughly with soap and water. Next it was cleansed with 70 per cent alcohol followed by ether in order to provide a dry surface. The cement used in conjunction with the Padgett dermatome was applied, and after it had dried, a layer of skin approximately 0.008 inch in thickness was removed from either side of the animal. Bleeding was controlled by pressure with gauze moistened with warm physiologic saline solution. As soon as the bleeding was controlled, the donor

site on one side of the animal was treated with a preparation of one of the following substances:

1. Triple dye compound
2. Sulfadiazine in triethanolamine with methocel
3. Thrombin and thrombin with fibrinogen
4. Paraffin
5. 10 per cent tannic acid
6. 5 per cent silver nitrate
7. 10 per cent tannic acid plus 5 per cent silver nitrate
8. Quebracho tannin

On the opposite side of each dog vaseline gauze dressings were applied to the similar donor site. Biopsies were taken from both wounds in each animal before application of the medicament and at approximately two, six, ten, and twenty-four hours after. In a few animals biopsies were taken more frequently and for longer periods of time than twenty-four hours. All biopsy specimens were fixed in 10 per cent formalin, embedded in paraffin, and stained with hematoxylin and eosin.

MICROSCOPIC OBSERVATIONS

*Triple Dye.**—Examination of the biopsies removed after two hours from donor sites on which triple dye had been placed revealed collections of fibrin and red blood corpuscles on the exposed surface of the corium. On this surface and between the collagenous bundles, small brownish granules were found. The superficial collagenous fibers adjacent to the granules presented a homogeneous appearance and were poorly outlined while the bundles in the deeper portions of the corium were sharply separated (Fig. 2). In the biopsies removed after four hours of treatment with the dye, almost one-half of the entire corium presented a homogeneous acidophilic appearance interrupted by irregular crevices. Only at the innermost portion of this homogeneous zone were normal collagenous fibers recognized. A few focal collections of leucocytes were seen about the vessels near the advancing edge of the eschar; these were granulocytes and lymphocytes. Hair follicles found in the homogeneous mass showed a marked loss of staining qualities. In the several sections available for examination at the end of six hours the lesion was little different from that seen at the end of the four-hour period (Fig. 3). In contrast, biopsies from donor sites covered by vaseline gauze showed, two to six hours after preparation of the site, small collections of fibrin and red blood cells on their dermal surface and normal collagenous bundles (Fig. 4).

Sections taken ten hours after application of the dye showed the eschar to be still thicker. It appeared as a dense, deeply staining mass sharply separated from the collagenous bundles of the deeper portion of the corium. The brittleness of the eschar was demonstrated by fragmentation produced by the microtome knife. Within the eschar,

*Two per cent gentian violet, 1 per cent brilliant green, and 0.1 per cent neutral acriflavine.

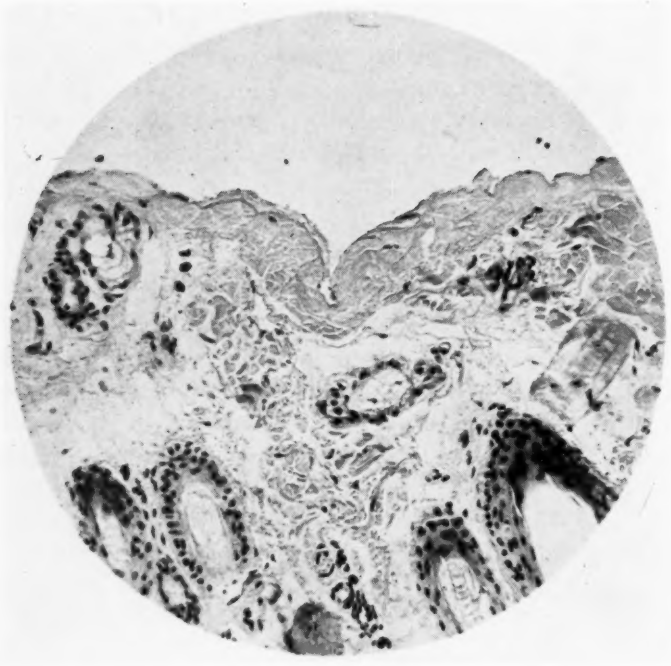


Fig. 2.—Donor site two hours after treatment with triple dye; note superficial homogeneous zone (magnification ×175).

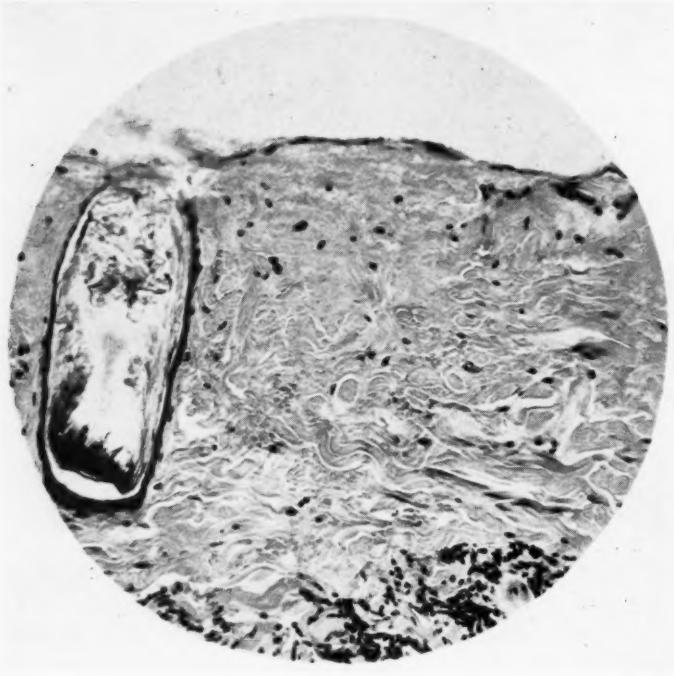


Fig. 3.—Donor site six hours after treatment with triple dye; note early eschar formation (magnification ×175).

remnants of hair follicles were present, and at the edge numerous perivascular focal collections of leucocytes were found.

In sections taken twenty-four hours after the application of the dye, the eschar had extended through almost the entire dermis. The leucocytic exudate had increased to form a thick layer of cells extending into the subcutis. Numerous hair follicles were enmeshed in the brittle eschar, which was separating at many points from the underlying normal corium (Fig. 5). The donor sites covered by vaseline-impregnated gauze showed no evidence of damage to the collagenous fibers (Fig. 6).

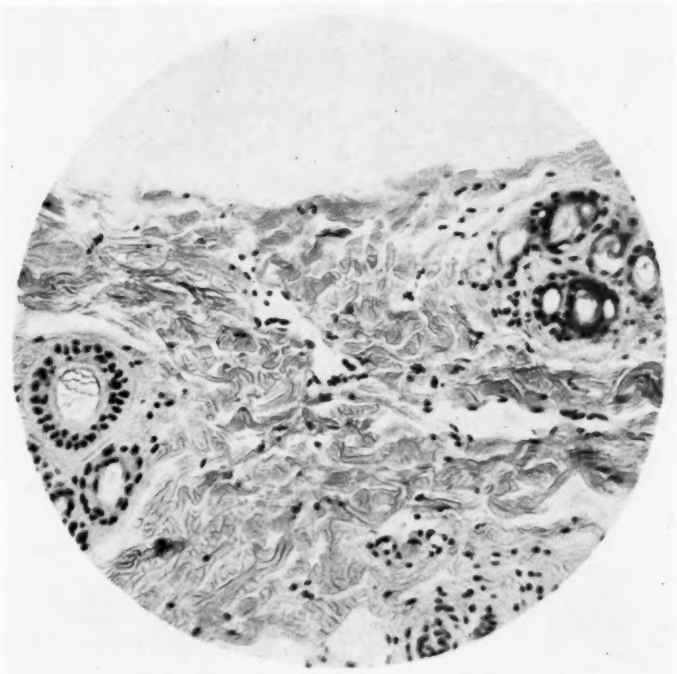


Fig. 4.—Donor site at six hours, covered by vaseline gauze; note well-preserved collagenous fibers (magnification ×175).

One case in a human being in which triple dye had been applied to a prepared donor site was available for study. In the biopsy obtained one hour after its application the dye had provoked an exudate of fibrin and many red blood corpuscles. A comparable site treated with vaseline gauze showed little reaction. Six hours after application of the dye a rather marked exudate of fibrin and red blood corpuscles was seen on the surface of the wound. The eschar production in the dye-treated wound was evidenced by the appearance of a homogeneous, deeply staining, acidophilic zone. No leucocytic infiltration was yet in evidence. At six hours comparable wounds treated by vaseline gauze showed comparatively little reaction.

Examination of biopsies obtained at the end of fourteen hours showed the donor site which had been treated with vaseline gauze to be moder-

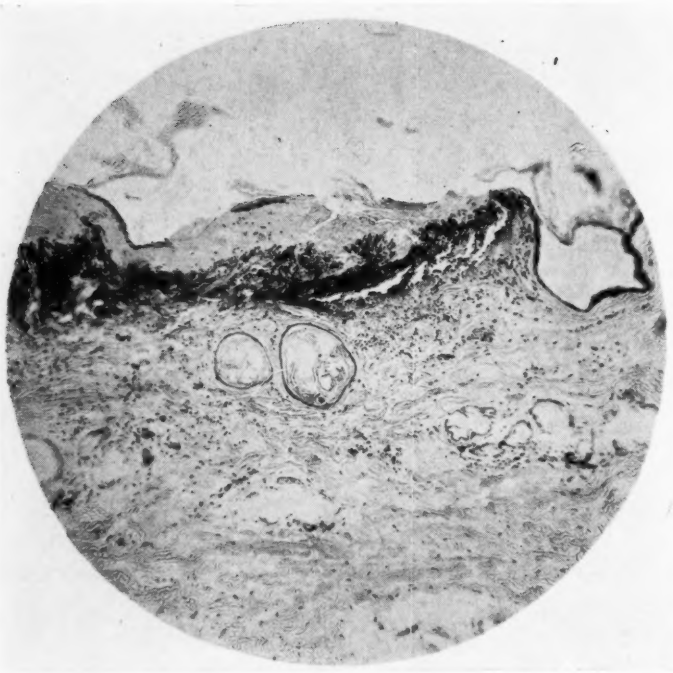


Fig. 5.—Eschar produced by triple dye at twenty-four hours (magnification ×100).

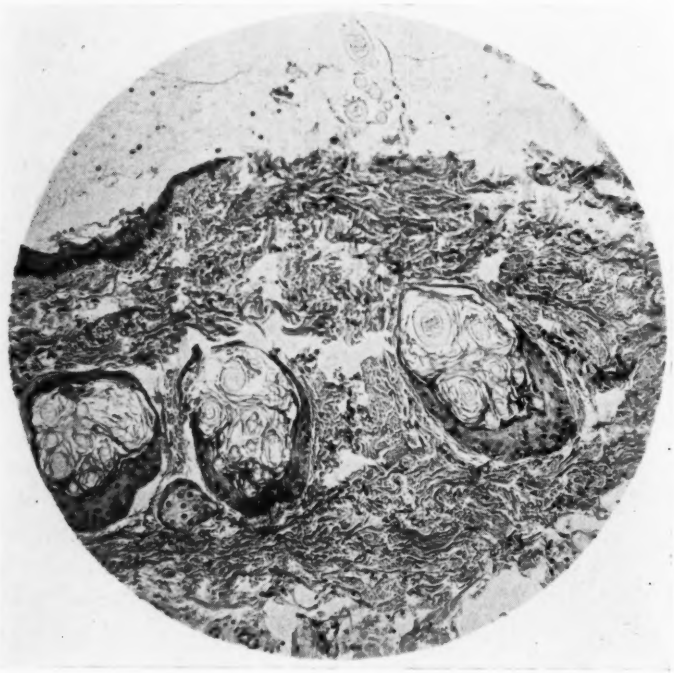


Fig. 6.—Donor site at twenty-four hours, covered by vaseline gauze; note lack of damage to dermis (magnification ×150).

ately infected, and numerous leucocytes were seen on the surface of the dermis. In contrast, a brittle eschar had formed on the wound treated by the triple dye, and the superficial portion of the dermis was almost replaced by this deeply staining homogeneous mass. Beneath it large collections of leucocytes were present.

*Sulfadiazine in Triethanolamine With Methocel.**—Eight donor sites were prepared for the application of this material, and opposite control sites were prepared for vaseline gauze. In biopsies obtained at two hours only small clumps of fibrin and a few red blood corpuscles were found on the surface of the dermis. The most superficial collagenous bundles were indistinct and appeared to coalesce. Between them an eosin-staining fluidlike material containing small granules was observed. In sections taken at four hours these bundles of collagenous fibers appeared to fuse, and the entire area stained more uniformly with eosin. An exudate made up of small groups of granular leucocytes separated the damaged from the deeper normal collagenous fibers. Sections prepared from biopsies of the donor sites six hours after application of vaseline gauze showed only small collections of fibrin and leucocytes on the surface, but in biopsies taken from the wounds treated by sulfadiazine in triethanolamine with methocel, the now familiar changes found in eschar production were observed. The most superficial collagenous bundles were deeply staining and almost homogeneous. Collagenous fibers immediately beneath the deeply staining area were almost indistinct, and about them focal collections of leucocytes were present. The damage to the dermis was variable in extent in all biopsies and was not always uniform in the same tissue section.

Examination of the biopsies removed ten hours following therapy revealed only a continuation of the previously related process, characterized by an increased penetration of the triethanolamine compound, destruction of hair follicles, and an increased leucocytic exudate. From twenty-four to thirty hours following therapy a large portion of the corium was destroyed by production of a brittle eschar, which eschar was apparently shattered by the microtome knife. In addition, an intensive leucocytic exudate was seen beneath the eschar and about the homogeneous collagenous fibers which had been damaged by the medicament.

It was possible to obtain biopsies from a human donor site treated by the triethanolamine compound at three, twelve, and thirty hours after treatment. The tissue reaction and formation of the eschar varied little from that seen in dogs. In the biopsies at three hours there was a mild fibrinous and leucocytic exudate present on the surface of the dermis. The collagenous fibers stained normally. At twelve hours, however, the superficial bundles had been converted into a narrow homogeneous eosin-staining zone, at the base of which a few leucocytes were present. In sections prepared from the biopsies thirty hours after

*Sulfadiazine 1.5 per cent, triethanolamine 5 per cent, aerosol OT. 0.1 per cent, methocel 1.67 per cent, sodium benzoate 0.2 per cent, and water q. s. ad 100 per cent. Furnished by Lederle Laboratories, Inc. New York.

application of the medicament the eschar was practically identical with that found in the biopsies taken at the end of the twenty-four-hour period.

Thrombin and Thrombin With Fibrinogen.*—Examination at two hours of sections from wounds covered by thrombin revealed on the surface a marked exudate of red blood corpuscles. A few leucocytes and small quantities of fibrin were also present. The application of thrombin and fibrinogen reduced the erythrocytic exudate, and the dermal surface was found to be covered with a loosely adherent eosin-staining granular mass. It seemed to push into the adjacent collagenous bundles but produced no evident tissue changes. In the biopsies taken after four to six hours, few additional changes were noted in the sections. In certain areas some collagenous bundles showed mild retrogressive changes and were surrounded by small collections of leucocytes. Similar retrogressive changes were noted when a donor site was covered by vaseline gauze or left untreated. In biopsies taken ten to twenty-four hours after application, numerous leucocytes were found on the dermis and throughout the superficial portion of it while the collagenous bundles often showed retrogressive changes. These findings were attributed to infection of the donor sites.

Paraffin.†—Examination of sections from donor sites covered by paraffin showed no damage to the dermis after two to four hours. The only constant finding was an increased number of granular leucocytes between the more superficial collagenous fibers. In sections taken after six hours the donor sites showed no evidence of tissue destruction nor alteration apparently due to the applied paraffin.

10 per cent Tannic Acid; 5 per cent Silver Nitrate; 10 per cent Tannic Acid plus 5 per cent Silver Nitrate; and Quebracho Tannin.‡—After comparing the biopsies from the donor sites treated by the above agents we concluded that the tissue changes produced were similar; hence these medicaments will be considered as a group in the following descriptions. In the biopsies taken after two hours of therapy these tanning substances were found as brown to brownish-black masses of refractile granules on the surface of the freshly denuded corium and between its collagenous bundles. Some of the material was also found in the incised hair follicles. In many of the sections the more superficial collagenous bundles stained more intensely and appeared glossy; these changes were interpreted as the earliest evidence of damage to the dermis.

Sections taken six hours following application of the tanning agents showed their deeper penetration between the collagenous bundles. The affected fibers now stained deeply with eosin and appeared as a com-

*Purified thrombin from beef plasma diluted with water to give 5,000 units per cubic centimeter. Furnished by Parke, Davis & Co., Detroit, Mich.

†Paraffin wax 670 Gm., petrolatum 250 Gm., liquid petrolatum 150 Gm., cod liver oil 50 c. c, sulfanilamide powder 50 Gm., menthol 1 Gm., camphor 1 Gm., and oil of eucalyptus 1 c. c.

‡Quebracho tannin, 7½ per cent in a water-soluble base and dihexylin 1:1000 (meta-di-hydroxy-di-secondary-hexyl-benzene). Furnished by Parke, Davis & Co., Detroit, Mich.

pact homogeneous mass containing many hair follicles and sebaceous glands. This newly formed eschar was separated from the deeper normal corium by a thick layer of leucocytes. Biopsies taken from donor sites treated by vaseline gauze showed only a slight reaction to the medicament and surgical trauma. Small masses of fibrin and clusters of red blood cells were seen on the surface of the wounds. There was no evidence of tissue destruction.

Biopsies from donor sites treated by tanning agents showed striking changes after twenty-four hours of therapy. Beneath the tanning agents the eschar appeared as a structureless acidophilic mass separating at numerous points from the more normal dermis. These lines of separation were often limited by an intense leucocytic exudate which was embedded in collagenous bundles showing marked retrogressive changes. In subsequent biopsies these collagenous bundles formed a part of the complete eschar or slough, and complete re-epithelization occurred beneath them. In the wounds treated by vaseline gauze a varying degree of leucocytic extravasation probably dependent on secondary infection was found. Notably there was a little damage to the dermis and very little exudate between the collagenous bundles.

Examination of the donor sites at forty-eight hours showed them to be infected because of difficulty in keeping the dressings intact and the wounds clean. Tanning agents had produced extensive damage with destruction of the corium to a great depth, leaving undamaged only a thin strip of collagenous bundles and in some sections only the fatty subcutis. Vaseline gauze-treated wounds showed some damage to the superficial portions of the dermis, damage probably due to the observed infection.

DISCUSSION

Agents that produce a firm eschar have been used extensively in the treatment of burns. Although many advantages are cited favoring the use of such medicaments, very little attention has been given either to the clinical complications or to the tissue changes resulting from the application of eschar-forming agents. We are more concerned at present with the latter problem.

Since its introduction in 1927, tannic acid[2] has been used widely in the treatment of burns. Aldrich,[3] in 1933, applied aniline dyes which he believed formed an eschar superior to that formed by tannic acid, since (1) the eschar did not crack, (2) there was an instantaneous analgesia, and (3) the eschar supposedly sterilized the burn by neutralizing bacteria. He was of the opinion that burn "toxemia" paralleled infection. After some experience Aldrich added brilliant green and acriflavine to gentian violet solution to prevent the growth of gram-negative organisms. More recently, in 1941, Pickrell[4] advocated the use of 3 per cent sulfadiazine in 8 per cent triethanolamine to be sprayed upon burned areas. This likewise forms an eschar and in most instances prevents infection. Rothman and his co-workers[5] have just

reported a group of cases in which the patients were treated in a similar manner and exhibiting few infections.

Several investigators[6, 7] have studied the effects of tannic acid and similar medicaments on experimental burns, and their work has suggested that eschar-forming agents may delay healing. Clinical tests[8] have also been made wherein various agents were tested on donor sites of man, and we were able to obtain biopsies from prepared human donor sites which permitted a comparison of tissue reactions to several tanning agents and to vaseline gauze. In order to test further the medicaments used in burn therapy we placed them on prepared donor sites of dogs, and we have been able to study the reactions of normal tissue to the medicaments in serial biopsies. The procedure discussed in this paper should be useful in estimating the deleterious effects of any substance that might be used on burned surfaces. The demonstration that most of the agents commonly employed in the treatment of burns have the ability to destroy normal tissues and thereby increase the depth of the burn, demands that one question the wisdom of employing them. If they are used, one must be certain that the beneficial effects offset the harm done by the increased tissue damage.

It may be that in the future a substance will be supplied having all the features desired for the treatment of burns. From these studies we may well wonder whether any material can be found which will become closely enough adherent to the surface of a fresh wound or burned area without damaging normal tissues. At present it would seem that eschar-forming agents produce the eschar over burned surfaces by necrotizing normal tissues. In order to stick to a moist surface without combining with the surface and thereby damaging it, an inert substance would have to form a mechanical union with the cells of the epidermis or with the collagenous bundles of the corium. The existence of a material having the capacity to form such a union seems highly unlikely. The alternative is to maintain a nonirritating substance over the burn by a suitable dressing or adhesive attached to adjacent normal structures.

REFERENCES

1. Hirshfeld, John W., Pilling, Matthew A., and Maun, Mark E.: A Comparison of the Effects of Tanning Agents and of Vaseline Gauze on Fresh Wounds of Man, Surg., Gynec. & Obst. **76**: 556-561, 1943.
2. Davidson, Edward C.: Tannic Acid in the Treatment of Burns, Surg., Gynec. & Obst. **41**: 202-221, 1925.
3. Aldrich, R. H.: Role of Infection in Burns; Theory and Treatment With Special Reference to Gentian Violet, New England J. Med. **208**: 299-309, 1933.
4. Pickrell, K. L.: New Treatment of Burns; Preliminary Report, Bull. Johns Hopkins Hosp. **69**: 217-221, 1941.
5. Rothman, Milton, Tamerin, Joseph, and Bullowa, Jesse G. M.: Treatment of Burns With 2.5 Per Cent Sulfadiazine in 8 Per Cent Triethanolamine Solution, J. A. M. A. **120**: 803-805, 1942.
6. Taylor, Frederic: The Misuse of Tannic Acid, J. A. M. A. **106**: 1144-1146, 1936.
7. Anagnostidis, Nikos: Histologische experimentelle Untersuchungen über die Wirkung einzelner örtlich angewandter Arzneimittel bei Verbrennungen dritten Grades, Deutsche Ztschr. f. Chir. **252**: 248-256, 1939.
8. Conn, Bradford, and Cope, Oliver: Rate of Epithelial Regeneration, Ann. Surg. **117**: 85-92, 1943.

THE RELATIONSHIP OF ACUTE ANEMIA TO WOUND HEALING

An Experimental Study*

E. L. Besser, M.D., and J. L. Ehrenhaft, M.D., Iowa City, Iowa
(From the Departments of Surgery, Pathology and Internal Medicine, University of Iowa School of Medicine)

IN REVIEWING the literature on wound healing, one frequently finds statements to the effect that wounds do not heal well in patients with anemia.[1-4] We were unable to find any experimental work to substantiate or disprove this postulate.

Certain systemic factors are known to influence wound healing. It has been shown that vitamin C is necessary for the production of collagen.[5, 6] Both experimental studies and clinical observations have shown that an adequate intake of vitamin C is necessary for normal wound healing.[6-9] Epithelial healing is delayed when there is a deficiency in vitamin A.[2] When hypoproteinemia exists, fibroplasia is decreased, wound healing is delayed, and eviseration is common.[10-13]

The problem of anemia and wound healing presents two aspects: first, the relation of acute anemia to wound healing, and, second, the relation of chronic anemia to wound healing. Chronic anemia is often found in debilitated patients who also have vitamin deficiencies or hypoproteinemia. Since it is definitely established that these latter factors influence wound healing, and chronic anemia usually does not exist without some degree of these other deficiencies, it is difficult to draw conclusions from patients of this group. Acute blood loss from traumatic wounds or extensive operations causes acute anemia which is usually uncomplicated by other deficiency states. In a series of cases in which the patients developed shock during operative procedures at the University Hospitals, dextrose-citrate plasma was found to be efficacious in the treatment of this condition.[14] In certain cases, whole blood loss had been marked, and there was a resultant acute anemia. Our interest was aroused as to whether the course of these patients would be as satisfactory as if they had been given whole blood transfusions to combat both red cell and plasma loss. The question arose—would their wounds heal as readily? It was felt that this problem could be adapted to experimental study.

Experimental Procedure.—The first extensive studies of tensile strength of wounds in experimental animals were carried out by

*This study was made with the cooperation of Dr. Elmer DeGowin of the Department of Medicine. The blood chemical determinations were carried out by Dr. Irving Friedman.

Received for publication, March 1, 1943.

TABLE I

EXPERIMENTAL DATA CONCERNING THE RELATIONSHIP OF ACUTE ANEMIA TO WOUND HEALING

DAYS POST-OPERATIVE	EXP. NO.	EST. BLOOD VOL.* (C.C.)	AMT. BLED (C.C.)	PLASMA GIVEN (C.C.)	HEMATOCRIT† (PER CENT)			PLASMA PROTEINS (GM. PER 100 C.C.)			TENSILE STRENGTH (MM/HG)	AVERAGE TENSILE STRENGTH
2ND DAY SERIES					BO	PO-1	PO-2	BO	PO-1	PO-2		
Anemic dogs	1	800	660	550	51		20	5.94	5.95		48	
	2	880	600	450	51		19	5.42			62	55
Control dogs	1	800			43			6.49			100	
	2	1000			43			5.94			106	103
3RD DAY SERIES					BO	PO-1	PO-3	BO	PO-1	PO-3		
Anemic dogs	1	1080	850	500	39	20	24	7.17	6.04	5.36	74	
	2	920	800	500	41	21	19	6.45	6.48	5.97	34	
	3	1360	1150	950	41	16	17	6.56	6.33	5.56	60	56
Control dogs	1	1200			50						50	
	2	1520			53						50	
	3	1600			55						74	
	4	700			38		40.5	5.66		5.73	82	
	5	750			44		45	5.87		6.35	50	
	6	1200			52			6.12			54	60
4TH DAY SERIES					BO	PO-1	PO-4	BO	PO-1	PO-4		
Anemic dogs	1	720	550	550	50	24	24	5.95	5.80	6.04	45	
	2	680	570	600	43	17	20	4.95	5.77		50	
	3	700	550	450	41	23	22	5.68	5.94	6.74	62	52
Control dogs	1	1200			49		47	5.45		5.68	88	
	2	720			48		50	6.23		5.94	70	
	3	1152			38		36	6.27		6.54	36	62
5TH DAY SERIES					BO	PO-1	PO-5	BO	PO-1	PO-5		
Anemic dogs	1	680	450	400	50	22	24	5.70	5.80	5.90	64	
	2	840	650	625	52	19	23	6.30	6.10	6.30	76	
	3	1040	780	700	54	25	27		6.0	6.10	55	
	4	680	500	550	50	14		6.45	6.20	6.0	52	
	5	850	560	320		34	35	5.98		5.92	100	65
Control dogs	1	680			50			6.20			72	
	2	680			51			5.90			52	
	3	960			53						80	68

6TH DAY SERIES					BO	PO-1	PO-6	BO	PO-1	PO-6		
Anemic dogs	1	750	575	525	46	17	21	6.41	5.94	5.97	80	
	2	600	500	450	48	19	22		5.05	5.95	118	99
Control dogs	1	720			47		45	6.28		5.94	92	
	2	800			46		46	5.06		5.45	116	104
7TH DAY SERIES					BO	PO-1	PO-7	BO	PO-1	PO-7		
Anemic dogs	1	1600	400	360	50	40	45		6.30		195	
	2	720	500	480	52	32	38		5.60	5.80	180	
	3	720	500	450	50	30	36	6.10	6.20		185	
	4	640	400	350	54	31	35		5.90		148	
	5	880	640	550	54	11	16	6.45	6.10	6.20	154	
	6	860	750	700	48	14	20	5.40	5.80	5.70	172	
	7	840	640	500	53	12	17	6.10	5.90	6.20	150	
	8	1680	1100	1000	52	19	22	5.80	5.80	5.60	148	166
Control dogs	1	640			49						160	
	2	1100			51			6.20			200	
	3	800			39		44			5.76	250	
	4	1440			47		46			5.71	172	
	5	680			43		39	5.35		5.51	172	190
9TH DAY SERIES					BO	PO-1	PO-9	BO	PO-1	PO-9		
Anemic dogs	1	880	700	480	52	25	26.5	5.92	4.89	6.06	260	
	2	1150	820	750	47	21	28	5.29	6.10	5.69	264	262
Control dogs	1	750			43		44	8.55		6.19	164	
	2	640			38		48	4.97		6.01	290	227
11TH DAY SERIES					BO	PO-1	PO-11	BO	PO-1	PO-11		
Anemic dogs	1	840	700	450	48	20	36	7.11	6.00	7.18	300	
	2	800	600	600	39	18	30	5.90	6.19	6.43	210	255
Control dogs	1	930			50		47	6.08		6.43	170	
	2	880			42		44	5.64		5.28	276	223

*Blood volume was estimated as 8 per cent of body weight.

†BO—Before operation; PO—postoperative days.

Harvey and Howes[4, 15] and their co-workers. They found that the tensile strength was dependent upon the growth and maturation of the fibroblast and noted that after a lag period of three to five days, fibroplasia began abruptly and proceeded with decreasing velocity until a maximal strength was reached about the twelfth to fourteenth day. In most of these experiments, small incisions were made in the stomachs of guinea pigs or rats and the wounds were closed with 000 plain catgut. The tensile strengths were determined by distending the stomachs with air. Other investigators have used this method with slight modifications and have found similar curves for the tensile strength of healing wounds.[16-18]

Our experiments were carried out on stock dogs of varying sizes and ages. The dogs were fed adequate and uniform diets. While consistent results were reported by those who distended the entire stomachs of guinea pigs or rats, we found that distending the entire stomach of the dog resulted in wide variations. It was felt that these differences were based largely on the variations in the size of the stomachs. Therefore, we found it expedient to open the stomach and place the incision to be tested over the open end of an Erlenmeyer flask, and this fixed area of stomach was then distended by air under manometric control. Our procedure was as follows: Two incisions, each 4 cm. in length, were made through all layers of the stomach wall. One incision was made near the pylorus and was used for determination of tensile strength. The other incision was made in the cardia and this was used for microscopic study. Suture material consisted of 0000 plain catgut. A continuous Lembert suture was used to approximate the muscularis and submucosa. The serosa was closed by three interrupted sutures. The abdominal wound was closed with silk. The animals were killed on subsequent days and the tensile strength of the incisions determined as described above. Twenty-six dogs were used as controls. Acute anemia was produced in twenty-six dogs by withdrawing blood from the femoral artery. The plasma was immediately replaced at the time by intravenous infusion of pooled plasma from donor dogs. Hematocrit and total protein determinations were made preoperatively, on the day following operation, and on the day when the tensile strength determination was carried out. These data are given in Table I. Vitamin C levels were determined in the early experiments. The dogs, however, were fed on known adequate diets for several weeks prior to operation, and the levels were consistently normal. It was thought unnecessary to continue these determinations.

Results.—There was no significant change in plasma proteins between the pre- and postoperative levels. The anemia produced varied from moderate to extreme, and, in most instances, was below the levels usually found clinically in cases of hemorrhage. The curves of tensile strengths of the incisions in relation to days following operation are shown in Fig. 1. These curves have the same general configura-

tion as those reported by Howes and Harvey[4] and other workers.[15-18] Immediate tensile strength of the sutured wound was between 150 and 200 mm. of mercury. A lag period occurred until the fourth or fifth day, and a rapid increase in tensile strength then followed during the sixth and seventh days. It was found that the mean values

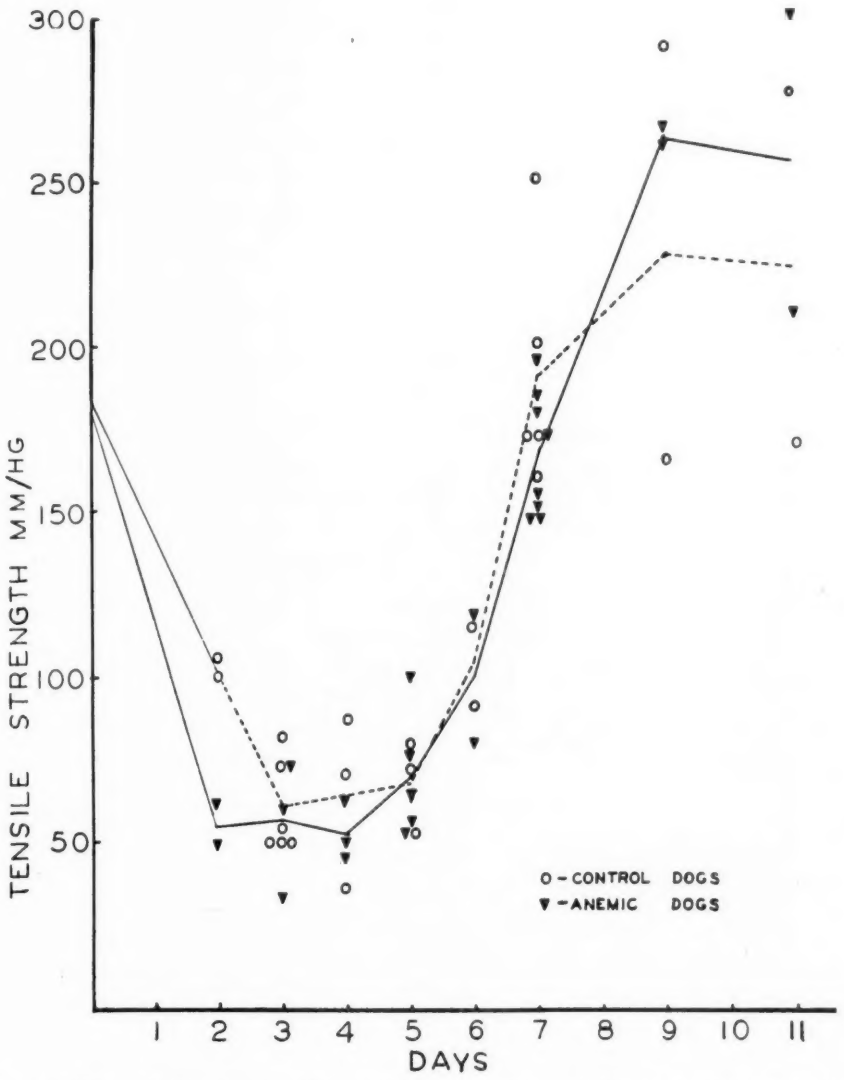


Fig. 1.—The relationship of acute anemia to wound healing as shown by tensile strength of incisions in the stomach of the dog.

of the tensile strengths of the incisions in the anemic and control dogs showed no significant differences. Although experimental error is considerable in this type of procedure, the values overlap and the averages are close.

Microscopic studies showed essentially the same picture in both the anemic and control dogs. Fibroplasia could be seen on the second

day. The fibroblasts were bridging across rapidly until the fifth day, at which time bridging seemed complete, and this coincides with a rapid rise in tensile strength on this day. On the sixth day, definite contraction of the wound had occurred and inflammatory reaction was minimal. Some interstitial fibrillar material could be seen as early as the seventh day. On the ninth day and eleventh day, newly formed fibrous tissue appeared to be very dense and firm. Epithelium started to bridge across on the second day and was fused by the third day. Glandular formation was seen about the ninth day.

The dogs recovered from the anemia rapidly and by the eleventh day the hematocrit values were nearly normal. Therefore, it was felt unnecessary to carry the experiments further than eleven days post-operatively.

DISCUSSION

When whole blood is unobtainable, plasma is being used extensively in treating shock due to hemorrhage in military surgery and to a lesser extent in civil practice. These experiments suggest that the acute anemia found as the result of this procedure does not retard wound healing. This should not be interpreted as complete endorsement of the use of plasma rather than whole blood in the treatment of shock due to hemorrhage since it has not yet been proved that acute anemia does not have other detrimental effect, such as lowering the resistance of the patient to infection.

SUMMARY

Acute anemia produced in dogs does not retard wound healing as shown by determination of tensile strength and microscopic study. The clinical significance of this finding has been discussed.

REFERENCES

1. Glenn, Frank, and Moore, S. W.: The Disruption of Abdominal Wounds, Surg., Gynec. & Obst. **72**: 1041, 1941.
2. Arey, Leslie B.: Wound Healing, Physiol. Rev. **16**: 327, 1936.
3. Mason, Michael: Wound Healing, Internat. Abstr. Surg. **69**: 303, 1939.
4. Howes, E. L. and Harvey, S. C.: The Clinical Significance of Experimental Studies in Wound Healing, Ann. Surg. **102**: 941, 1935.
5. Wolbach, S. B.: Controlled Formation of Collagen and Reticulum: A Study of the Source of Intercellular Substance in Recovery from Experimental Scorbutus, Am. J. Path. **9**: 689, 1933.
6. Wolfer, J. A.: The Surgical Aspect of Vitamin C Deficiency, S. Clin. North America **20**: 225, 1940.
7. Lanman, T. H., and Ingalls, T. H.: Vitamin C Deficiency and Wound Healing, Ann. Surg. **105**: 616, 1937.
8. Wolfer, J. A., and Hoebel, F. C.: The Significance of Cevitamic Acid Deficiency in Surgical Patients, Surg., Gynec. & Obst. **69**: 745, 1939.
9. Holman, Emile: Vitamin and Protein Factors in Pre-Operative and Post-Operative Care of the Surgical Patient, Surg., Gynec. & Obst. **70**: 261, 1940.
10. Thompson, W. D., Raydin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption, Arch. Surg. **36**: 500, 1938.
11. Thompson, W. D., Raydin, I. S., Rhoads, J. E., and Frank, I. L.: Use of Lyophile Plasma in Correction of Hypoproteinemia and Prevention of Wound Disruption, Arch. Surg. **36**: 509, 1938.

12. Rhoads, J. E., Fliegelman, M. T., and Panzer, L. M.: The Mechanism of Delayed Wound Healing in the Presence of Hypoproteinemia, J. A. M. A. **118**: 21, 1942.
13. Koster, Harry, and Shapiro, Arthur: Serum Proteins and Wound Healing, Arch. Surg. **41**: 723, 1940.
14. Besser, E. L.: Stored Dextrose-citrate Plasma in the Treatment of Operative Shock, Arch. Surg. **43**: 451, 1941.
15. Harvey, Samuel C.: The Velocity of the Growth of Fibroblasts in the Healing Wound, Arch. Surg. **18**: 1227, 1929.
16. Ellis, J. D.: The Rate of Healing of Electro-Surgical Wounds as Expressed by Tensile Strength, J. A. M. A. **96**: 16, 1931.
17. Botsford, T. W.: The Tensile Strength of Sutured Skin Wounds During Healing, Surg., Gynec. & Obst. **72**: 690, 1941.
18. Bricker, E. M., and Graham, E. A.: The Inhibitory Effect of Sulfanilamide on Wound Healing, J. A. M. A. **112**: 2593, 1939.

MALIGNANT NEOPLASMS OF THE SPLEEN

Review of the Literature and Report of a Case of Primary Lymphosarcoma (Reticulum-Cell Type)

Paul F. Hausmann,* M.D., and Fred W. Gaarde,† M.D.
Rochester, Minn.

At the Boston City Hospital,[31] out of a total of 4,000 surgical procedures, splenectomy was performed only twice for primary splenic malignant disease. Smith and Rusk, in 1923, extensively reviewed the literature and added two cases to the 102 recorded instances of such malignant disease. Of this number, in twenty-two cases the condition was described as lymphosarcoma; two of the cases had been reported from the Mayo Clinic.

Careful review of the literature subsequent to 1923[1-4, 6-11, 18, 19, 21, 23, 24, 27, 28, 34, 35, 39, 40, 41] revealed reports of forty-five additional corroborated cases of splenic malignant disease, including nine of lymphosarcoma.[5, 12, 13, 16, 17, 22, 30, 33] Reports of twenty other cases were indexed but had been printed in journals that were not available. If this latter group is accepted, the total is brought to 169. Two cases of lymphosarcoma[15, 26] and seven others of malignant disease of the spleen in which the diagnosis was confirmed histologically at the clinic,[37, 38] brought the total of known cases of all types of malignant splenic neoplasms to 178, of which thirty-three were lymphosarcomas.

We report a case of primary reticulum-cell lymphosarcoma of the spleen which we recently observed.

REPORT OF CASE

A tall, thin merchant, 38 years old, registered on Aug. 20, 1940. The following history was elicited.

From January to April, 1940, the patient had had vague, unreferred and momentary epigastric pain which occurred at any time of day. In April, immediately after a late night lunch, he had experienced severe sharp pain in the left shoulder and boring pain in the left upper abdominal quadrant. This pain caused him to writhe and toss all night but it subsided by morning, leaving a residual tenderness which continued for two or three days. The results of physical examination and roentgenologic examination of the stomach, gall bladder, and colon carried out at that time elsewhere were negative. The man was then free from symptoms until July 31, 1940, three weeks prior to registration, when he experienced slight pain in the left shoulder and severe pain in the left upper abdominal quadrant for which administration of morphine and hospitalization were necessary. Further roentgenologic examination elsewhere revealed in the left upper abdominal quadrant a

*Fellow in Surgery, Mayo Foundation.
†Division of Medicine, Mayo Clinic, Rochester, Minn.
Received for publication, Feb. 24, 1943.

tumor which was causing deformity of the splenic flexure of the colon. After the attack of pain, slight residual tenderness persisted in the left upper quadrant and was present when the patient was admitted to the clinic.

Physical examination yielded only the following positive findings: There was an occasional coarse râle in the apex of the left lung anteriorly. Small, soft, nontender inguinal nodes were palpated bilaterally. The region of the left upper abdominal quadrant was tender to deep palpation and on deep inspiration—the lower margin of the spleen, which was firm and smooth, could be felt but with difficulty. Percussion over the left lumbar region was moderately painful.

Roentgenograms revealed an extrarenal mass in the left upper abdominal quadrant.

Examination of the blood revealed nothing abnormal. The results of serologic tests were negative as were those of the urinalysis, microscopically, although albumin, grade 1, on the basis of 1 to 4, was present.

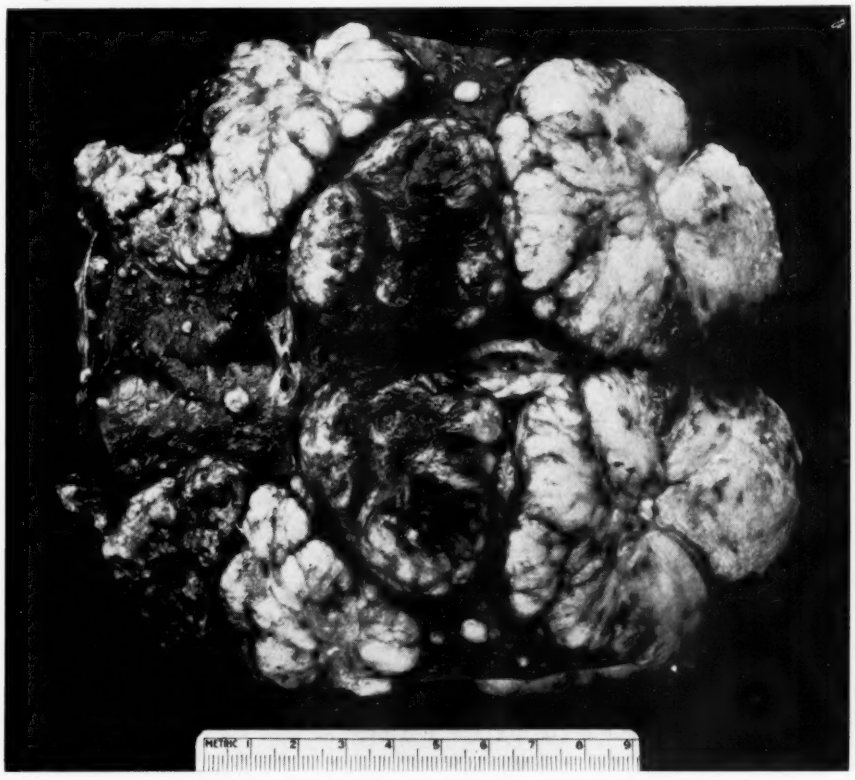


Fig. 1.—Gross appearance of surface of reticulum-cell lymphosarcoma of spleen, made by sectioning.

On Aug. 23, 1940, surgical operation was performed. The spleen was round, tense, and enlarged to about four times normal size. Splenectomy was difficult because of adhesions to the undersurface of the diaphragm. There was no evidence of extension of disease to any of the other abdominal organs or of involvement of any of the lymph nodes.

Convalescence was uneventful and the patient was dismissed from the hospital on the fourteenth postoperative day. Roentgen therapy over both upper abdominal quadrants and over both inguinal regions was given. On his return to the clinic for further roentgen therapy on Oct. 16, 1940, approximately two months post-

operatively, there was no evidence of extension or of generalization of disease and his only complaints were of occasional slight pains over the incision and of residual weakness. He had gained fourteen pounds (6.4 kg.). Small, soft, inguinal nodes were still palpable but not enlarged.

The spleen weighed 810 Gm. and measured 14 by 12 by 7 cm. It was firm and reddish, with firm yellowish nodules easily visible beneath the surface of the capsule which was everywhere smooth and unbroken except on the diaphragmatic surface where it was roughened by several dense fibrous adhesions. The capsule was not invaded anywhere by neoplastic tissue. Cut surfaces (Fig. 1) revealed numerous round and oval, yellowish-brown nodules, 1 mm. to 8 cm. in diameter, almost completely replacing the normal splenic parenchyma, which was recognizable only as narrowed, compressed, reddish-brown bands coursing between the oval yellowish masses. There were no regions of hemorrhage or of degeneration.

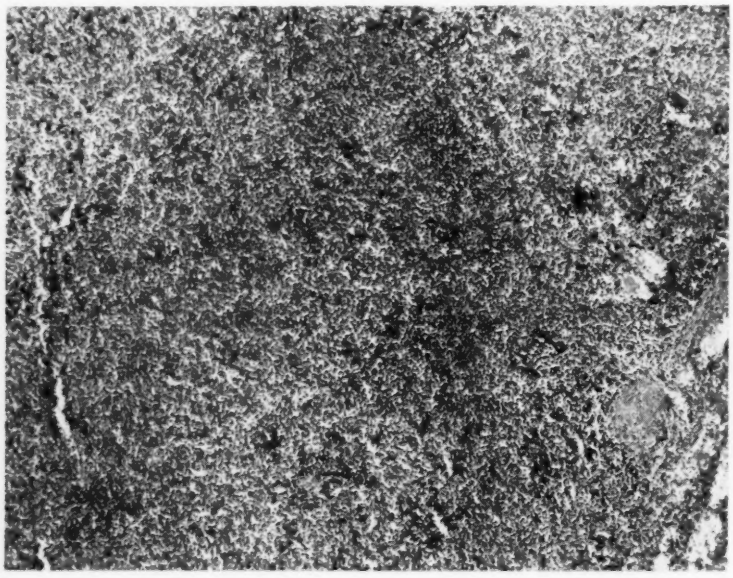


Fig. 2.—Reticulum-cell lymphosarcoma of spleen; only a small strand of recognizable splenic architecture can be noted (magnification ×55).

Histologically, as in the gross, only a few small regions of recognizable splenic parenchyma containing scattered malpighian corpuscles were observed (Fig. 2). The remainder of the tissue consisted of undemarcated, solidly packed, round cells, slightly larger than mature lymphocytes, retaining none of the architectural characteristics of splenic or of lymphoid structure. Here and there, small blood vessels were visible, and in a few regions evidence of hemorrhage into the tissue was seen. Only a few vestiges of fibrous trabeculae remained. Under high magnification (Fig. 3) it was seen that the tumor cells were about twice the size of lymphocytes and that they contained hyperchromatic nuclei with large nucleoli. The cytoplasm, large in amount, had the "misty" appearance described as characteristic of the cells of reticulum.

On Feb. 7, 1941, the patient returned to the clinic. For five or six weeks he had had transient dull and sharp pain in the left upper abdominal quadrant and pain in the epigastrium. He had lost twenty pounds (9.1 kg.) since his last visit and weakness was so pronounced that he had spent most of the past month in bed.

Physical examination revealed two hard lymph nodes about the size of walnuts, in the left supraclavicular fossa, and a questionable mass in the left upper abdom-

inal quadrant, but there were no other nodal enlargements. Palliative roentgen therapy was given over the two regions and the masses disappeared. The patient left the clinic in two weeks somewhat stronger but the subsequent course of his disease was gradually downward, and on July 7, 1941, he died at his home.

CLASSIFICATION OF MALIGNANT SPLENIC NEOPLASMS

Much of the confusion which exists regarding the terminology employed in designating the histologic diagnosis in reported cases of malignant disease of the spleen could be obviated if it were remembered that there are four types of tissue in the spleen from which tumors can arise. Enumerated in outline form, these tissues are:

I. The capsular and trabecular framework from which arise fibroma, fibrosarcoma, and spindle-cell sarcoma.

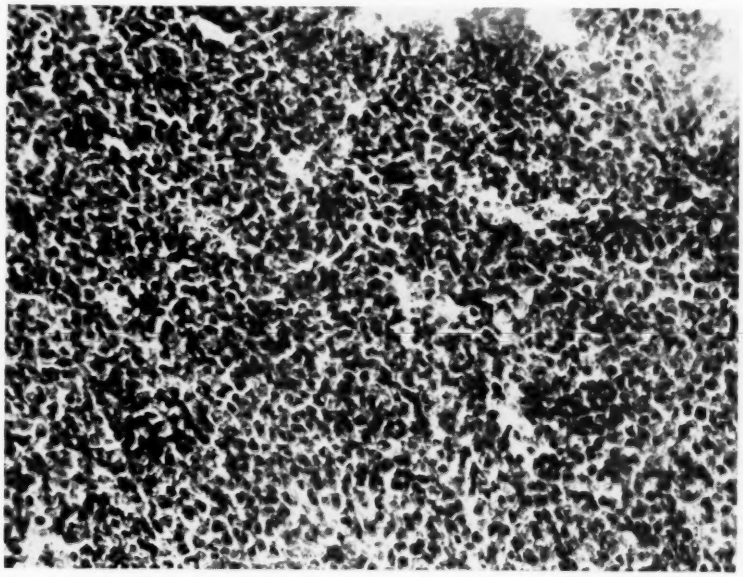


Fig. 3.—Characteristic tumor reticulum cells (magnification ×210).

II. The lymphoid elements which give rise to lymphoma and lymphoblastoma. Lymphoblastomatous tumors we choose to classify further as follows:

A. Lymphosarcoma.

1. Large round-cell (reticulum-cell type).
2. Small round-cell (lymphoblastic type).
3. Giant lymph follicle hyperplasia.

B. Hodgkin's granuloma.

III. The vascular or sinusal endothelium from which arise angiomas as well as their malignant counterparts, endothelioma, endothelial sarcoma, and angiosarcoma.

IV. The reticulo-endothelial system, or portion of the framework of the spleen, which gives rise to splenic enlargement in the syndromes of

Gaucher, of Niemann-Pick, and of Christian, and to reticulo-endothelioma and reticulo-endothelial sarcoma.

Although there is not any tissue in the spleen from which carcinoma might arise, primary carcinoma of the spleen was reported in the medical literature prior to 1923. Unless the theory of embryonic cell rests is accepted, and an authentic instance of such a rest has not been observed, the diagnosis must be regarded as untenable.

There are observers who distinguish sharply between lymphosarcoma and giant lymph follicle hyperplasia. We have included the latter as a subclassification of lymphosarcoma until further knowledge allows its classification elsewhere.

Analysis of the available accounts of primary malignant lesions in forty-five cases, reported from 1923 through 1940, established the incidence of the various types of splenic neoplasms (Table I).

TABLE I

INCIDENCE OF MALIGNANT NEOPLASMS OF THE SPLEEN IN 45 CASES, 1923-1940 INCLUSIVE

GROUP	DIAGNOSIS	CASES	TOTAL
	Primary carcinoma	1	1
I	Primary sarcoma	8	
	Large round-cell sarcoma	7	
	Small round-cell sarcoma	1	
	Unspecified round-cell sarcoma	2	18
II	Lymphosarcoma	9	
	Reticulum-cell sarcoma	1	
	Giant lymph follicle hyperplasia	3	13
III	Endothelioma	1	
	Endothelial sarcoma	1	
	Angioblastoma	1	
	Angiosarcoma	3	
	Hemangio-endothelioma	3	
	Malignant hemangioma	1	10
IV	Reticulo-endothelioma	1	
	Reticulo-endothelial sarcoma	2	3
	Total		45

The pathologist's diagnosis in the cases of splenic neoplasm observed at the clinic, not including the two cases of lymphosarcoma reported prior to 1923, are recorded in Table II.

TABLE II

PATHOLOGIC DIAGNOSIS IN NINE CASES OF SPLENIC NEOPLASM

GROUP	DIAGNOSIS	CASES	TOTAL
I	Primary sarcoma	1	
	Fibrosarcoma	3	4
II	Lymphosarcoma	1	
	Reticulum-cell lymphosarcoma	1	
	Giant lymph follicle hyperplasia	1	3
III	Endothelial sarcoma	1	1
IV	Reticulo-endotheliosis	1	1
	Total		9

In spite of the varied terminology employed by different authors, all of the reported tumors were included easily and conveniently in one of four groups of our outline according to the tissue from which they sprang. The pathologic diagnosis thus served to indicate the predominance of a particular type of cellular element or the degree and direction of differentiation of the tumor. The greatest variation of nomenclature was observed in descriptions of the neoplasms which we have listed in group III, a fact which might justify MacCallum's hesitancy to accept endothelioma because of his fear that its inclusion would prove to be a wastebasket for unusual tumors lacking characteristics permitting ready recognition.

The only reported instance of primary carcinoma of the spleen[36] from the years 1923 to 1940, inclusive, which we were able to find concerned a patient whose first demonstrable lesion was a nodule on a buttock. Necropsy revealed extensive carcinomatous infiltration of the liver and spleen. Inasmuch as convincing evidence of primary origin of the disease was not presented, the carcinoma of the spleen, in our opinion, must be regarded as metastatic from an unrecognized primary lesion.

The predominant number of tumors were included in group I (Table I) although, as was pointed out by Smith and Rusk, many tumors of this group could be classified as lymphosarcoma, since small round-cell sarcoma is practically indistinguishable from the lymphoblastic type, and the large round-cell sarcoma is identical with the reticulum-cell type of lymphosarcoma. Accepting this fact, it appears that subsequent to 1923, as prior to this date, lymphosarcoma has been the type of primary splenic malignant disease most commonly encountered.

Sex incidence in the cases reviewed by Smith and Rusk was fifty-one men and thirty-two women; in twenty-one instances, the sex was not stated. Cases of malignant splenic neoplasm reported subsequently elsewhere included seventeen men and eighteen women, whereas at the clinic there were five men and four women. In the cases of lymphosarcoma reported elsewhere five patients were men and four were women, while both patients observed at the clinic were men.

The average age of patients in cases reported elsewhere, subsequent to 1923, was 46.7 years; in the majority the disease occurred in the fifth and sixth decades. The average age of the patients who were reported as having lymphosarcoma was 43.6 years; the majority were in the sixth decade. The patients observed at the clinic averaged 52.3 years; most of them were in the seventh decade. Both patients who had lymphosarcoma were 62 years old.

In contrast to incidence of malaria in 13 per cent of cases reported prior to 1923, there was an incidence of only 4.4 per cent of malaria in cases reported subsequently. Of the patients observed at the clinic, one of nine, or 11 per cent, gave a history of malaria, and he was one of the two who had lymphosarcoma.

Syphilis was present in 4 per cent of the cases in the series reported by Smith and Rusk, in 4.4 per cent of the series reviewed by us, and in 33.3 per cent of cases (nine) seen at the clinic. None of the patients who had lymphosarcoma were syphilitic.

In 2 per cent of the series of Smith and Rusk, there was a history of tuberculosis, but tuberculosis had not existed in any of the subsequent cases, either in those reported in the literature or in those observed at the clinic.

SURGICAL PROCEDURES

Splenectomy was performed in eighteen of forty-five cases reported in the literature in the years 1923 through 1940. Four of the splenectomized patients died within the first thirty hours after operation, and of the remaining fourteen patients, two died within a year from generalized involvement of lymph nodes, in one case the disease being lymphosarcoma and in the other, giant lymph follicle hyperplasia. Twelve of the patients were living and well at the time the cases were reported, the periods of survival ranging from thirty days to eight years.

Exploratory laparotomy was performed in four cases but in each case the disease was found to be too extensive to justify surgical intervention. Splenectomy was possible in seven of the nine cases observed at the clinic, including both cases of lymphosarcoma. One of the seven patients died immediately postoperatively and the survival periods of four others were nineteen days, three months, nineteen months, and four years, respectively. The patient with giant lymph follicle hyperplasia had generalized involvement of the lymph nodes five months after operation, but he received roentgen therapy one, four, and six years postoperatively and was living and well more than seven years after splenectomy. One of the patients who had lymphosarcoma survived splenectomy three months and died of metastases to bones and brain without involvement of lymph nodes; the other patient was living and well, without evidence of recurrence or metastasis, when last heard from in February, 1940, four years after removal of the spleen. Exploratory laparotomy in two cases revealed fibrosarcoma too extensive for splenectomy, so that only biopsy was done.

STATISTICAL COMMENT

It has been repeatedly observed that the lymphoblastomas, particularly lymphosarcomas, are multicentric in origin, frequently involving almost simultaneously many lymph nodes, in various anatomic situations; namely, the cervical, axillary, mediastinal, and inguinal regions, as well as the spleen, the gastrointestinal tract, and the abdominal lymph nodes.

In an attempt to determine whether isolated splenic lymphosarcoma is a precursor of generalized lymphosarcomatosis and therefore to be regarded as a part of the generalized process, or whether it is a similar

condition which is confined to the spleen, the following statistics were obtained.

Of the nine cases of splenic lymphosarcoma reported in the literature, there was generalized involvement of the lymph nodes of the groin within one year in only one case.[29] In another case,[16] the disease was generalized when the patient first was examined, but because of the immense size of the spleen, the condition was reported as primarily splenic. Metastasis to the spinal cord, without lymph nodal enlargements, was present in another case.[12] In two instances there was extension to adjacent structures; Krumbhaar[22] reported involvement of liver, pancreas, stomach, and bladder, whereas Gerundo and Miller[14] noted extension to the diaphragm. In a case reported by Cabot, Mallory hesitated to state whether the tumors were primary in the stomach or in the spleen, both of which were involved. One of Frank's patients died twenty-four hours after splenectomy, and the other patient died eight months postoperatively. In the second case[32] the cause of death was unstated, but the disease was not generalized. In another case the extent of disease was not noted postoperatively. In two of nine cases, or 22.2 per cent, primary lymphosarcoma, therefore, was a precursor of lymphosarcomatosis.

In one of the two cases reported from the clinic prior to 1923,[15, 25] lymph nodal involvement took place within four months postoperatively. The other patient lived more than seven years without evidence of recurrence. One of two patients observed at the clinic, subsequent to 1923, died within three months of metastasis to the bone and brain, without lymph nodal involvement. The other patient, as stated previously, was living and well without any evidence of recurrence four years postoperatively. In only one of the four cases studied at the clinic, or 25 per cent, did lymphosarcomatosis develop subsequent to splenectomy for what was thought to be a primary splenic neoplasm. In the case reported herein, generalized involvement of nodes was not present and it is problematic whether the lesions in the supraclavicular nodes were metastatic or gave evidence of the multicentricity of the disease.

Review of the three closely related instances of giant lymph follicle hyperplasia which are reported in the medical literature discloses that one patient[20] had generalized involvement within one year after splenectomy; another,[26] who had nodes in the groin at the time splenectomy was performed, died four hours after operation; the third patient survived four years and succumbed, finally, to recurrence in the left upper abdominal quadrant. The results in these cases reveal generalization of involvement in two of three, or 67 per cent, of cases.

The only patient with giant lymph follicle hyperplasia who was observed at the clinic, as mentioned earlier, had involvement of lymph nodes in the groin and axilla within three months after splenectomy,

but was alive and well at the time this paper was written, seven years postoperatively.

CONCLUSIONS

1. Although the series of cases of lymphosarcoma studied was not large enough to permit any final conclusions to be drawn, in the light of the figures in the preceding paragraphs, splenectomy appears justifiable for lymphosarcoma confined to the spleen.

2. The number of cases of giant lymph follicle hyperplasia studied in this series was small, also, but it appears that although the disease usually progresses more slowly than lymphosarcoma, the condition is more likely to become generalized.

REFERENCES

1. Adam, Ludwig: Primäre Milzgeschwulst, Zentralbl. f. Chir. **55**: 481-484, 1928.
2. Beasely, B. T.: Sarcoma of the Spleen, J. M. A. Georgia **13**: 395-396, 1924.
3. Berman, Adolf: Ein Fall von primärem Milzsarkom, Wien. klin. Wchnschr. **37**: 1237-1238, 1924.
4. Biller, S. B.: Primary Endothelioma of the Spleen, Arch. Path. **25**: 534-538, 1938.
5. Cabot Case 15311: Case Records of the Massachusetts General Hospital, Clinicopathological Exercises, New England J. Med. **201**: 228-229; Discussion 229-231, 1929.
6. Caldwell, G. T.: Endothelioma of the Spleen With Report of a Case, South. M. J. **26**: 120-125, 1933.
7. De Brun, H. C. W. S.: Primary Sarcoma of the Spleen, New York M. J. **118**: 85-88, 1923.
8. De Fourmestraux, M. J.: Tumeur de la rate. Splénectomie, Bull. et mém. Soc. de chirurgiens de Paris. **49**: 941-943, 1923.
9. De Navasquez, S.: Angioblastoma of the Spleen With Metastases in the Liver, J. Path. & Bact. **42**: 651-656, 1936.
10. Del Buono, Pietro: Alterazioni dello secheletro nell 'emo-angiosarcoma della milza, Radiol. med. **19**: 609-630, 1932.
11. Eickenbusch, F.: Ein Fall von primärem Sarkom der Milz, Frankfurt. Ztschr. f. Path. **35**: 464-476, 1927.
12. Ferrando, Hugo, and Saloz, Hugo: Some Interesting Cases From the Medical Clinic of the University of Geneva, With Remarks on Pathology and Diagnoses, Internat. Clinics, **3**: 223-258, 1923.
13. Frank, Louis: Sarcoma of the Spleen, Am. J. M. Sc. **183**: 77-81, 1932.
14. Gerundo, Michael, and Miller, M. B.: Reticulum-cell Sarcoma of the Spleen, Am. J. Cancer **35**: 528-533, 1939.
15. Giffin, H. Z.: Present Status of Splenectomy as a Therapeutic Measure, Minnesota Med. **4**: 132-138, 1921.
16. Grayzel, D. M.: Sarcoma of the Spleen; Report of Five Cases, Am. J. Cancer **36**: 237-242, 1939.
17. Howard, Tasker: Primary Sarcoma of the Spleen (Reticulum Celled), J. Lab. & Clin. Med. **14**: 1157-1161, 1929.
18. Jackson, R. H.: Quoted by Jones, A. P.[19]
19. Jones, A. P.: Unusual Spleen Cases, Ann. Surg. **109**: 960-969, 1939.
20. Kellert, Ellis: Lymphoblastoma of the Spleen, Am. J. Cancer **15**: 844-849, 1931.
21. Köhler, Hans: Ueber primäres Milzsarkom, Arch. f. klin. Chir. **135**: 194-202, 1925.
22. Krumbhaar, E. B.: The Incidence and Nature of Splenic Neoplasms With a Report on Forty Recent Cases, Ann. Clin. Med. **5**: 833-860, 1927.
23. Krumbhaar, E. B., and Scott, J. P.: Tumors, of the Spleen With a Report on Twenty-eight Recent Cases, S. Clin. North America **7**: 61-81, 1927.
24. Langenstrass, K. H., and Neumann, Meta: Reticulo-endothelial Sarcoma of the Spleen, Arch. Path. **20**: 752-759, 1935.
25. MacCallum, W. G.: A Textbook of Pathology, Ed. 5, Philadelphia, 1932, W. B. Saunders Company, 1036 pp.
26. Mayo, W. J.: Principles Underlying Surgery of the Spleen With a Report of Six Splenectomies, J. A. M. A. **54**: 14-18, 1910.

27. McNee, J. W.: Sarcoma of the Spleen, J. Path. & Bact. **39**: 83-88, 1934.
28. Orlandi, Noël: Primäres, diffuses Hämangioendotheliom der Milz, Virchows Arch. f. path. Anat. **269**: 152-159, 1928.
29. Paine, C. G.: Malignant Neoplasm of Spleen and Bone Marrow With Metastases in Liver, J. Path. & Bact. **34**: 139-142, 1931.
30. Sherwood, W. A., and Smith, A. L.: Primary Lymphosarcoma of the Spleen, Report of a Case, S. Clin. North America **7**: 1069-1078, 1927.
31. Smith, C. E., and Rusk, G. Y.: Endothelioma of the Spleen; a Study of Two Cases With Review of the Literature of Primary Malignancies of the Spleen, Arch. Surg. **7**: 371-414, 1923. .
32. Stevenin, Henri, Bergeret, Andre, Albot, Guy, and Lelourdy, Jean: Le réticulosarcome de la rate, Presse méd. **20**: 382-384, 1935.
33. Sturgeon, C. T., and Ware, E. R.: Primary Lymphosarcoma of the Spleen, S. Clin. North America **11**: 1163-1169, 1931.
34. Terzian, E.: Symptomatology and Diagnosis of Primary Sarcoma of the Spleen With the Report of a Case, M. J. & Rec. **128**: 526-528, 1928.
35. Ugriumow, B.: Über zwei seltene Fälle von Gefässneubildungen in der Milz und Leber, Virchows Arch. f. path. Anat. **259**: 366-372, 1926.
36. Werwath, K.: Über primäre maligne Milztumoren, Zentralbl. f. Chir. **62**: 2716-2719, 1935.
37. Wilson, L. B.: The Pathology of Splenomegaly: A Study of the Operative and Autopsy Material From the Mayo Clinic, Surg., Gynec. & Obst. **16**: 240-251, 1913.
38. Wilson, L. B.: Studies in the Pathology of the Spleen, Pathology of Spleens Removed for Certain Abnormal Conditions of the Blood, Col. Papers, Mayo Clin. **7**: 500-510, 1915.
39. Wright, A. W.: Primary Malignant Hemangioma of the Spleen With Multiple Liver Metastases, Am. J. Path. **4**: 507-524, 1928.
40. Wright, J. H., and Stevenson, E. M. K.: Case of Primary Sarcoma of the Spleen, Glasgow M. J. **114**: 1-9, 1930.
41. Zeno, Artenio, and Cid, J. M.: Hémangio-endothéliome de la rate, Ann. d'anat. path. **7**: 583-588, 1930.

THE USE OF CURARE IN THE TREATMENT OF TETANUS

Case Report

Stuart C. Cullen, M.D., and C. S. Quinn, M.D., Iowa City, Iowa

(From the Division of Anesthesiology, Department of Surgery and the Department of Medicine, State University of Iowa College of Medicine, Iowa City)

THE obstruction of breathing, the prolonged respiratory depression, the accumulation of mucus, and the infrequent changes of position associated with the use of tribromethanol with amylene hydrate (Avertin fluid*) for the control of the muscle spasm of tetanus predispose to pulmonary complications. With its use, there is difficulty in maintaining adequate nutrition because of the inability of the patient to eat and drink. Constant, close supervision by both nurse and physician is also essential. Although this means of controlling muscle spasm has proved beneficial in the treatment of persons affected with tetanus, it seems that control without such a marked general depression would be more desirable. In an attempt to simulate the latter state, curare was used on one patient.

CASE REPORT

The patient, H. H., a 48-year-old carpenter, entered the University Hospital Nov. 11, 1942, complaining of stiffness of the jaw and pain and stiffness of the back. He gave the history of having struck his finger with a hammer, breaking the skin, while working about a chicken coop five weeks before admission. The onset of symptoms occurred one week before admission. At that time the patient developed a tingling sensation in the right hand, followed by aching of the muscles of that arm. Several days later he noticed stiffness of the jaws which interfered with eating. The trismus progressed rapidly within a few hours, until he had difficulty opening his mouth. Soreness, stiffness, and aching pain appeared in the shoulder muscles two days before admission, and soon involved the muscles of the back and those of the chest.

The patient was a normally developed white man in a good state of nutrition. He was mentally clear, but appeared physically exhausted. He was dehydrated, and the mucous membrane of the mouth was slightly cyanotic. Spasm of the facial muscles had produced the classical risus sardonicus. Trismus prevented his opening his mouth more than 2 cm. between the upper incisors and the lower edentulous gum. His speech was thick, and he spoke with his hand to his jaw in attempt to lessen the great effort of opening his mouth. Inspection of the musculature showed spasm of the muscles of the jaw, neck, back, thorax, and abdomen, and hypertonicity of the extremities, with exaggerated reflexes. The pulse rate was 120 and the temperature not elevated. The respiratory rate was 25, and he breathed with effort. The leucocyte count was 11,050. With the exception of a small, almost healed laceration of the left index finger, the remainder of the examination was negative. A diagnosis of tetanus was made.

*Winthrop Chemical Company, Inc.

Received for publication, Feb. 6, 1943.

No sooner had the examination been completed than the patient had a paroxysm of painful muscular spasm. His body was straightened and then arched in opisthotonos. The jaw was tightly clenched, the abdomen rigid, and the extremities stiff. The thoracic and other respiratory muscles were fixed in a state of tonic contraction, so that respiratory movements ceased and cyanosis deepened. Relaxation sufficient to permit diaphragmatic motion occurred spontaneously within a few minutes. Similar spasms recurred every few hours.

COURSE AND TREATMENT

The patient was given 20,000 units of tetanus antitoxin intramuscularly, and 30,000 units intravenously, on the night of admission, followed by 50,000 units intravenously the next day. The small local lesion was opened, débrided, and dressed with zinc peroxide paste. For the first forty-eight hours the patient was given avertin per rectum. The degree of relaxation of the abdominal wall was used as a guide to dosage. The doses of the drug and time of administration are listed in Table I. In spite of marked general depression, intermittent spasms of the entire body still occurred, with clonic jerking of the extremities. There was considerable respiratory depression, obstruction, and mucous production. The latter was somewhat controlled with atropine.

Twenty-four hours after admission, the pulse rate, temperature, and respiratory rate began to rise, and, in another twenty-four hours, the pulse rate was 150, the temperature, 104° F., and the respiratory rate, 48. There were coarse râles in the bronchial tree. It was felt that the patient was probably developing pneumonia. The presence of pneumonic infiltration in the upper part of the right lung was later verified roentgenologically. Avertin was discontinued, and the administration of curare begun. The drug used was Intocostrin (extract of unauthenticated curare*). The drug was supplied as an extract, standardized by biological assay to contain the equivalent of 0.02 Gm. per cubic centimeter of a standard drug. It was administered either intravenously or intramuscularly. It is ineffective when given subcutaneously or perorally.

In this case there was no apparent difference in the duration of the effect produced by intravenous and intramuscular injection of curare. The onset of action was, of course, much more rapid with intravenous administration.

After the depression from avertin had disappeared, and the patient was conscious, the curare effect was spectacular. At the height of a spasm, when the patient was suffering excruciating pain, the intravenous injection of curare produced marked relief in a matter of seconds. One could see the jaw relax, the opisthotonos disappear, and the respirations become easier. It was gratifying to see the patient in a reactive state, able to cough, expectorate, drink, and move about in bed.

The day after the discontinuance of avertin administration, the temperature fell and the respirations became slower. No specific or chemotherapy was used for the pneumonia.

*The Intocostrin was supplied through the courtesy of E. R. Squibb & Sons.

As with avertin, the frequency of administration of curare was determined by the tone of the rectus abdominis. The doses used are shown in Table I. There seemed to be much variation in the length of

TABLE I

DATE (1942)	TIME OF ADMINISTRATION	DRUG	DOSAGE (MG. PER KG.)	MODE OF ADMINISTRATION	DURATION OF EFFECT	
					HR.	MIN.
11/7	9:05 P.M.	Avertin	50	P. R.*	2	00
11/8	11:05		40	P. R.	10	05
	9:00 A.M.		70	P. R.	5	00
	2:00 P.M.		100	P. R.	2	10
	4:10		30	P. R.	0	50
	5:00		30	P. R.	0	55
	5:55		30	P. R.	0	25
	6:20		30	P. R.	1	25
	7:45		70	P. R.	5	30
11/9	1:15 A.M.		100	P. R.	9	05
	10:20		100	P. R.	4	55
	3:15 P.M.	Curare	60	I.V.†	8	05
	11:20		40	I.V.	9	10
11/10	8:30 A.M.		60	I.V.	6	50
	3:20 P.M.		70	I.V.	1	45
	5:05		50	I.M.‡	2	32
	7:37		70	I.M.	1	51
	9:28		50	I.M.	2	28
	11:50		50	I.M.	4	26
11/11	4:16 A.M.		50	I.M.	2	29
	6:45		50	I.M.	3	45
	10:30		50	I.V.	3	12
	1:42 P.M.		50	I.M.	2	13
	3:55		50	I.M.	3	30
	7:25		50	I.M.	3	30
	10:55		50	I.M.	1	10
11/12	12:05 A.M.		25	I.M.	1	55
	2:00		50	I.M.	3	45
	5:45		50	I.M.	1	00
	6:45		50	I.M.	2	25
	9:10		50	I.M.	3	15
	12:25 P.M.		50	10 mg. I.V.: 40 mg. I.M.	2	30
	2:55		50	I.M.	2	50
	5:45		50	I.M.	2	30
	8:15		50	I.M.	3	50
11/13	12:05 A.M.		50	I.M.	4	37
	4:42		70	20 I.V.: 50 I.M.	3	22
	8:10		50	10 I.V.: 40 I.M.	8	10
	4:20 P.M.		30	I.M.	0	40
	5:00	Beta-erythroidine	500	I.V.	3	51
	8:51		300	I.V.	3	44
11/14	12:35 A.M.		300	I.V.	2	55
	3:30		300	I.V.	4	33
	8:03		300	I.M.	2	22
	10:25		300	I.V.	1	25
	11:50		300	I.V.	1	55
	1:45 P.M.		300	I.V.	3	33
	5:20		300	I.V.	2	57
	8:17		300	I.V.	3	13
	11:30		300	I.V.	9	30
11/15	8:35		300	I.V.		

*P.R., per rectum.
†I.V., intravenous.
‡I.M., intramuscular.

the intervals between attacks, as well as in their duration and severity. It was found, however, that usually 0.050 Gm. of curare would keep the patient comfortable and free from acute spasm for about three hours. The amount of drug administered was determined by the response of the patient. Roughly speaking, 0.008 to 0.010 Gm. per kilogram was satisfactory.

On the seventh day, the last of the supply of curare was used. Treatment was continued with beta-erythroidine, a drug similar to curare in its action. Three hundred milligrams of a ten per cent solution produced approximately the same effect as 0.050 Gm. of curare. With the injection of beta-erythroidine, the patient experienced a slight feeling of faintness. On two occasions, there was momentary fall in systolic blood pressure of about 30 mm. No fall in blood pressure was observed when curare was used.

Beta-erythroidine was not needed after the ninth day. By this time, the spasms were no longer severe enough to endanger the patient's life or even discomfit him. He was then given 4.5 gr. (0.240 Gm.) of phenobarbital daily, in divided doses.

Until late in the course of the disease, sedatives were used only occasionally to control restlessness and irritability. There was no objection to moderate use of morphine or barbiturates, but in this case they were seldom needed because the patient often lapsed into sleep after receiving curare.

Nutrition and hydration were maintained by giving fluids intravenously and a liquid diet. Difficulty in swallowing was never a prominent symptom in this case during the early stages of treatment, but the possibility of regurgitation and aspiration during a sudden severe spasm, as well as the great fluid loss with sweating, made us prefer the intravenous route.

The generalized hypertonicity was slow in leaving, and was still present to some extent when the patient was discharged on the eighteenth day.

DISCUSSION

The treatment of tetanus with curare is not a new idea. Curare was first usel in the treatment of tetanus in 1894, by Hoche.[1] Since that time, a small number of cases in which tetanus was treated with curare have been reported.[2-6]

Lack of a good, standardized preparation of curare has hindered the development of this treatment. Most of the preparations which have been used were obtained from independent pharmacologists who were interested in the drug, and hence have varied in potency and purity.

The site of action of curare is peripheral, rather than central. It is said to act by interrupting the synaptic transmission of nerve impulses at the myoneural junction by depressing the nicotinic action of acetylcholine, thus producing paralysis without central depression.

It is selective in its action, and affects the muscles of the body in the following order: (1) muscles innervated by cranial nerves, (2) muscles of the trunk and extremities, and (3) muscles of respiration (the diaphragm is the last to be paralyzed). It is this sequence of action which makes possible the release of the convulsive patient from the asphyxiating tonic fixation of the chest, without complete paralysis of the respiratory muscles.

The side actions of curare, namely the reported tendency to produce bronchial spasm and hypersecretion,[2] were not troublesome. When questioned after the injection of the drug, the patient expressed relief, and stated that otherwise his only sensation was one of great weakness.

Provisions were made for the relief of undue respiratory depression after the injection of curare or beta-erythroidine, although none occurred in this patient. An anesthetic face mask, rebreathing bag, and oxygen supply were immediately available for artificial respiration. Although it has been recommended[5] that a mechanical respirator of the Drinker type be on hand, the respiratory paresis after the administration of curare is so sudden in onset and short lived that, by the time the patient could be placed in the respirator, the respiratory paresis would be spontaneously relieved. Physostigmine and prostigmine, because of their ability to depress cholinesterase, are suitable for use in combatting undue respiratory depression from curare.

Since beta-erythroidine was used in the terminal stage of the disease, little can be said about the relative effectiveness of this drug and curare. The circulatory depressant effect of beta-erythroidine, which was evident in this case, is undesirable.

SUMMARY

The use of curare for the control of muscle spasm in a case of tetanus is reported. It is felt that curare possesses certain advantages, and this case is presented in the hope that it will stimulate further clinical investigation into the value of this therapeutic agent.

Since the submission of this paper for publication, curare has been used in the treatment of three additional cases of tetanus. All three terminated fatally. The experience gained in these later cases leads us to believe that curare will effectively control the muscle spasm. The experience emphasizes, however, the necessity of having an individual or individuals experienced in the actions of curare and the course of the disease who can devote his or their entire time to the patient in the early stages of the disease. The variations in the manifestations of the disease and the variations in the response to the curare make mandatory this constant supervision by trained personnel. With this supervision, curare should be effective in the treatment and possess the advantages of a patient awake, able to move, void, defecate, and respire freely.

REFERENCES

1. Hoche, A.: Use of Curarine in Tetanus, Centralbl. Neurol. **13**: 289-296, 1894.
2. West, Ranyard: Intravenous Curarine in the Treatment of Tetanus, Lancet **1**: 12-16, 1936.
3. Mitchell, J. S.: Case of Tetanus Treated With Curarine, Lancet **1**: 262, 1935.
4. Cole, L. B.: Tetanus Treated With Curare, Lancet **2**: 475-477, 1934.
5. Isaeson, S. E., and Swenson, S. A., Jr.: Curare in the Treatment of Tetanus, Nebraska M. J. **26**: 136-137, 1941.
6. Hale-White: Textbook of Pharmacology, London, 1901, P. Blakiston Son & Co., p. 199.

THE USE OF CURARE FOR THE IMPROVEMENT OF ABDOMINAL MUSCLE RELAXATION DURING INHALATION ANESTHESIA

Report on One Hundred and Thirty-One Cases

Stuart C. Cullen, M.D., Iowa City, Iowa

(From the Division of Anesthesiology, Department of Surgery, State University of Iowa College of Medicine, Iowa City)

SURGICAL manipulations within the abdomen are always facilitated by a state of complete muscular relaxation associated with quiet breathing and contracted intestine. If this state can be achieved without increased hazard to the patient during anesthesia or without predisposing toward undesirable postanesthetic sequelae, the added convenience to the surgeon expedites his work and directly contributes to a smoother, more complete, and more rapid convalescence of the patient. In an effort to simulate this ideal condition, curare was administered during inhalation anesthesia.

The popular concept of the principal usefulness of curare as a means of paralyzing the game of foraging South American Indians or as a demonstrating drug in the pharmacology laboratory is gradually being displaced by a succession of interesting and valuable clinical applications. Since 1857, it has been used practically in the treatment of convulsive states such as tetany, strychnine poisoning, and chorea.[1] Burman[2] has advocated its use in the treatment of spastic disorders. Bennett[3] has found it useful in controlling the frequency of fractures accompanying the convulsions of metrazol shock therapy. Through the publications and exhibits of the latter men, I was tempted in 1940, to use curare as a means of improving the relaxation of abdominal musculature during inhalation anesthesia. At that time, a few dogs were given curare. In doses giving abdominal muscle relaxation, they salivated profusely, had extreme respiratory depression and asphyxial convulsive movements. These effects deterred the clinical application of curare for this purpose. Interest was, however, restimulated on the appearance of the report of Griffith and Johnson[4] of its use in twenty-five patients anesthetized with cyclopropane. An ample supply of Intocostrin* (extract of unauthenticated curare) was obtained and administered to 131 patients. The drug was supplied as an extract standardized by biological assay to contain the equivalent of 0.02 Gm. per cubic centimeter of a standard drug.

*Through the courtesy of Dr. L. H. Wright of E. R. Squibb & Sons.

Received for publication, March 9, 1943.

PHARMACOLOGIC PROPERTIES

As early as 1865, Claude Bernard[5] described the action of the drug on the neuromuscular junction and confirmed the observations of Watterton and Brodie, in 1814, that asphyxia from respiratory paralysis was the cause of death. Brown and Feldberg[6] demonstrated that the drug interferes with the transmission of impulses across sympathetic ganglia. It is selective in its action, and affects the muscles of the body in the following order: (1) muscles innervated by cranial nerves, (2) muscles of the trunk and extremities, and (3) muscles of respiration (the diaphragm is the last to be paralyzed). Respiratory depression of central origin has been reported.[7] Smooth muscle is not affected. In the pure form, no significant direct effect on heart or peripheral circulation is noted. No analgesic or anesthetic action has been demonstrated. Its effect, when given intravenously, is obtained in one minute. When given intramuscularly, its maximum effect is obtained in ten to fifteen minutes. It is not effective when administered subcutaneously or perorally. It is said to be completely eliminated in about two hours by destruction in the liver and excretion through the kidney. The action of the drug is said to persist for but twenty to thirty minutes, but, as will be pointed out later, the muscular relaxation produced by curare during inhalation anesthesia lasts much longer. There is little cumulative action and the drug can be repeated relatively frequently. Overdose causes respiratory paralysis, and treatment for it is artificial respiration with oxygen. Physostigmine and prostigmine are of value in specific antidotal therapy because they inhibit choline esterase.

METHOD

The anesthetic procedure during which curare was employed was performed as usual. The patients were premedicated with morphine and scopolamine according to their requirements and the requirements of the agent to be employed. They were anesthetized by means of the carbon dioxide absorption technique to the first or second plane level of third stage anesthesia and maintained there. The curare was introduced intravenously about the time the skin incision was made so that by the time the peritoneum was opened, the full effect of the dose had been obtained. With the introduction of the curare, the flow of anesthetic agent was discontinued for a few minutes until the degree of respiratory depression was determined. The optimum effect desired was complete muscular relaxation and quiet intestine. If this was not achieved, intravenous injections were repeated at three- to five-minute intervals until the desired effect was manifest. Relaxation then usually persisted for 60 to 120 minutes, or until closure of the peritoneum. After relaxation was established, it was unnecessary to repeat the curare during the course of long operations. It was, however, frequently necessary to inject more curare for closure of the abdomen if the operative procedure lasted longer than forty-five minutes.

Except for two infants who received 0.004 Gm. and 0.006 Gm., respectively, the smallest initial dose was 0.04 Gm. and the largest initial dose 0.1 Gm. After more experience in estimating the initial amount required, the usual first dose for patients between 20 and 70 years old was 0.060 Gm. If this proved insufficient, 0.040 Gm. was added. If more drug was still indicated, 0.020 Gm. was added at three- to five-minute intervals until the optimal state was reached. Except in very resistant cases, 0.040 to 0.060 Gm. at the time of peritoneal closure was sufficient. The largest total dose (0.240 Gm.) was given over a three-hour period to a 39-year-old man who had a resection of a portion of the ileum and colon. The average total dose, excluding the two infants, was 0.0925 Gm.

EFFECTS

It was found from experience that the amount of drug necessary to produce the ideal abdominal state of muscular relaxation and quiet gut often appreciably depressed the respiration. This respiratory depression progressed to complete paresis in five patients for periods varying from two to five minutes. In the others, the depression was manifested by loss of intercostal muscle function and jerky diaphragmatic movements. These more severe degrees of depression persisted for only five to twenty minutes and relatively normal ventilation reappeared long before the abdominal muscle tonus returned. Artificial respiration with intermittent inflation of the lungs by manual compression of the rebreathing bag was all that was necessary in those patients having complete respiratory arrest. In the others in whom ventilation was incompetent, the inspiratory phase was accentuated by manual compression of the rebreathing bag. These experiences emphasize the necessity for an immediately available and efficient means of ventilating the alveoli with oxygen when curare is being used. During inhalation anesthesia by the carbon-dioxide absorption technique, it is a simple matter and causes little inconvenience and minimal hazard.

Undesirable circulatory effects resulting from the administration of curare were infrequent and limited to those cases in which large amounts were given in a short period of time. In these cases, the systolic blood pressure dropped 30 to 40 mm. and the pulse pressure diminished. The pulse was unaffected and recovery was prompt. In other cases, blood pressure and pulse responses were not appreciably different from the changes associated with cyclopropane anesthesia. There was some evidence that with unrelieved respiratory depression an accumulation of carbon dioxide caused an elevation in blood pressure. From the clinical experience gained in these cases, it would seem that curare exerts no direct effect on the peripheral circulation or the heart unless excessive doses are administered.

No studies were made of the effect of curare on the liver or kidneys. No thrombosis or phlebitis was noted in the veins used for injection, even when relatively frequent injections were made.

The postoperative course of these patients was unaltered. A lower incidence of pulmonary pathology was expected because of the opportunity to use a nonirritating gaseous agent which is quickly eliminated postanesthetically. An evaluation of this factor will be deferred until more patients have been studied. The nursing staff shared the enthusiasm of the surgeons for the use of the cyclopropane-curare combination because the patients awoke promptly and required minimal immediate postanesthetic care.

One death occurred in a 60-year-old man brought to the operating room in a moribund state with a wound dehiscence. He was anesthetized to the first plane of the third stage with cyclopropane and given 0.060 Gm. of curare intravenously for the extreme relaxation required to effect the secondary closure. He died of sudden circulatory failure ten minutes after the injection of the curare. A fulminating peritonitis was found at autopsy.

An interesting case in the series was that of a 44-year-old woman who was difficult to examine bimanually because of marked voluntary abdominal muscle spasm. Without premedication of any type, she was given 0.060 Gm. of curare intravenously in an attempt to produce muscular relaxation of the abdomen. With this dose, she had some ptosis and masseter muscle relaxation, but no significant decrease in recti muscle tone. After five minutes, she was given 0.040 Gm. of curare intravenously. She then promptly presented the same clinical picture as the dogs mentioned early in this article. There was complete respiratory paralysis, marked salivation, and muscular twitching. She was given artificial respiration with oxygen by face mask and manual compression of the rebreathing bag of a gas machine. Her blood pressure taken at this time was elevated 20 to 30 mm. over her original pressure, but the pulse was essentially unchanged. However, there was still insufficient abdominal muscle relaxation to permit satisfactory examination. At this point, and although effective voluntary respiration had not returned, she was given morphine sulfate, gr. $\frac{1}{6}$ (0.010 Gm.), and scopolamine, gr. $\frac{1}{150}$ (0.00045 Gm.), intravenously. Voluntary and efficient respiration was almost immediately resumed by the patient. Relaxation of the recti was somewhat improved and the results of the bimanual examination led the surgeon to feel that a vaginal hysterectomy was indicated. The patient was then anesthetized with cyclopropane and the operation and anesthetic procedure carried out without further untoward incident. With only first plane anesthesia, abdominal muscle relaxation was excellent.

This case was interesting because it seemed to indicate that one of the premedicating drugs, probably scopolamine, is necessary for the uncomplicated use of the curare. It helps to explain why the dogs, which were unpremedicated, behaved in such a discouraging fashion. The case also indicates that complete abdominal muscular relaxation is difficult to achieve with curare alone in safe dosages, and that,

in addition to providing the necessary analgesia, the inhalation agent contributes a significant share in the production and maintenance of that relaxation.

OPERATIVE PROCEDURES AND ANESTHETIC AGENTS AND TECHNIQUES

In Table I are listed the operative procedures performed on the patients included in this report. It will be noted that all are procedures requiring excellent relaxation and quiet intestine, a state which cannot usually be obtained with gaseous agents alone. The two infants, on whom the Rammstedt procedure was done, were anesthetized by procaine infiltration of the line of incision, but because of the crying and straining, it was extremely difficult to restore the intestine to the peritoneal cavity. Small doses of curare intravenously permitted nontraumatic and easy restoration of the bowel to the abdominal cavity. Two patients had nitrous oxide anesthesia. One was a man, 72 years of age, who had a gastric resection, and the other a woman 62 years of age, who had an exploratory laparotomy. Curare successfully provided the relaxation which could not be achieved with the impotent nitrous oxide. Curare was also used to provide relaxation for the closing of an abdomen on one patient in whom the motor effect of the spinal anesthesia was wearing off.

TABLE I

OPERATIONS	NO.
Cholecystectomy	19
Mikulicz resection of the sigmoid	5
Choledochostomy	4
Gastric resection	13
Abdominoperineal resection of the rectum	5
Cholecystgastrostomy	1
Hysterectomy	29
Colostomy	4
Closure perforated peptic ulcer	2
Exploratory laparotomy	14
Total gastrectomy	1
Appendectomy	3
Resection of colon	2
Ureteronephrectomy	1
Incisional herniorrhaphy	9
Excision internal iliac aneurysm	1
Secondary closure abdomen	1
Ureterosigmoidostomy	1
Closure of enterovaginal fistula	1
Resection of ileum	3
Inguinal herniorrhaphy	1
Gastroenterostomy	2
Rammstedt operation	2
Oophorectomy	2
Abdominal sterilization	1
Uterine suspension	1
Relief of acute intestinal obstruction	1
Ureterolithotomy	1
Dilatation and curettage, examination under anesthesia	1

Four patients were given curare in conjunction with ether anesthesia. Two of these patients had no significant respiratory depres-

sion, but the other two had pronounced and prolonged respiratory depression from moderate amounts of curare. As a consequence of this experience, curare is not used in patients to whom ether is administered. This interesting effect is now being investigated. The remaining 122 patients were given cyclopropane. This combination appeared particularly effective. The scope of usefulness of cyclopropane was extended because it could be used for anesthesia for surgical procedures requiring extreme relaxation. The hazard of cardiac arrhythmia was reduced because it was no longer necessary to use high concentrations in an effort to secure relaxation.

SUMMARY

In an effort to secure improved abdominal muscle relaxation and quiet intestine with inhalation anesthesia, particularly by cyclopropane, curare was used in 131 patients. A brief review of the history and pharmacologic actions of the drug, as well as a report of its use on these patients, was included. Experiences of Griffith and Johnson[4] are confirmed by this report, and warrant its continued experimental use. These reports also indicate the need for extended investigation into the effect of curare in combination with other agents.

Since the submission of this article for publication, curare has been used in 370 additional cases. The results continue to be quite satisfactory. With this added experience, it has been possible to estimate better the required dose and obtain the desired state without marked respiratory depression.

REFERENCES

1. West, Ranyard: Intravenous Curarine in Treatment of Tetanus, Lancet **1**: 12-16, 1936.
2. Burman, M. S.: Therapeutic Use of Curare and Erythroidine Hydrochloride for Spastic and Dystonic States, Arch. Neurol. & Psychiat. **41**: 307-327, 1939.
3. Bennett, A. E.: Preventing Traumatic Complications in Convulsive Shock Therapy by Curare, J. A. M. A. **114**: 322-324, 1940.
4. Griffith, Harold R., and Johnson, Enid: The Use of Curare in General Anesthesia, Anesthesiology **3**: 418-421, 1942.
5. Bernard, C.: Note Sur la Curarine et Ses Effets Physiologiques, Bull. gén. de thérap. **69**: 23, 1865.
6. Brown, G. L., and Feldberg, W.: Differential Paralysis of the Superior Cervical Ganglion, J. Physiol. **86**: 10P, 1936.
7. Felger, J.: The Action of Curare on the Respiratory Center, J. Physiol. **100**: 417-422, 1942.

PRELIMINARY OBSERVATIONS CONCERNING PARAVERTEBRAL INJECTION OF THE SYMPATHETIC SYSTEM IN HYPERTENSION

HENRY G. SCHWARTZ, M.D., AND THOMAS FINDLEY, M.D., ST. LOUIS, MO.
(From the Departments of Surgery and Medicine, Washington University School of Medicine)

IT CAN no longer be doubted that sympathectomy with section of the splanchnic nerves is an effective adjunct in the treatment of some cases of hypertension, but there is no agreement concerning the type of operation which should be employed. The technique advocated by Peet[1] consists of bilateral supradiaphragmatic resection of the tenth, eleventh, and twelfth thoracic ganglia and the intervening chain, together with the splanchnic nerves; in a series of 290 patients, it produced a significant reduction in blood pressure in 51.4 per cent and satisfactory symptomatic improvement in 96.6 per cent.[2] The operation popularized by Adson and co-workers[3] consists of subdiaphragmatic removal of the splanchnic nerve and the first and second lumbar sympathetic ganglia; in a series of 224 patients, it resulted in a significant blood pressure reduction in 31 per cent and produced satisfactory symptomatic improvement in more than 80 per cent.[4] Smithwick[5] has advocated a combination of these two procedures. Whatever procedure is employed, the effect on blood pressure is often disappointing. However, all authors have noted frequent subsidence of papilledema and have stressed the fact that neither the degree of symptomatic improvement nor the amount of retinal healing is proportional to the drop in blood pressure.

In a much more limited experience we too have been impressed by the lack of correlation between the severity of symptoms and the height of the blood pressure. It is obvious that the surgical treatment of hypertension would be on a firmer basis if there were a more reliable method for identifying preoperatively those patients in whom good results will be obtained. The criteria suggested to date have not been particularly successful. This report concerns three patients upon whom bilateral paravertebral alcoholic blocks were performed for this purpose. We believe that the effects of novocain injection alone would be too transitory to allow adequate evaluation of any response.

The technique followed was similar to that described by White[6] for injection of the upper thoracic trunk in the treatment of angina pectoris

Received for publication, Nov. 11, 1942.

but modified to effect roughly those areas denervated by the combined Peet and Adson operations; i.e., the tenth, eleventh, and twelfth thoracic segments, first lumbar segment and the splanchnic nerves. After light morphine-scopolamine analgesia was produced, spinal needles were inserted at the appropriate levels, first on the right side about three fingerbreadths lateral to the midline; they were passed just below the lower borders of the transverse processes or articulating portions of the ribs and then directed medially at an angle of 20 to 30 degrees to a depth of 3 to 3½ cm. beyond the level of the rib articulations. At this depth, the needle point comes to rest against the anterolateral surface of the vertebral bodies where the ganglionated chain lies. In the case of the splanchnic nerves themselves, their point of entry between the medial and intermediate crura of the diaphragm lies very close to the vertebral body. Customary precautions were taken to make sure that the needle tips did not lie within the pleural space, blood vessels, or intervertebral foramina. Injection of 2 c.c. of 1 per cent solution of procaine hydrochloride at each level was followed by the slow instillation of 3 to 4 c.c. of 80 per cent alcohol. Both sides were injected at a single sitting. In the two male cases, the second lumbar segment was also injected on the right side and probably should be included bilaterally. Completeness of injection was then determined by means of a sweat test, using cobalt chloride as an indicator.

CASE REPORTS

CASE 1.—G. H., a 29-year-old white man, had suffered for more than ten years from attacks of headache, vertigo, nausea, and transient amaurosis. For six months prior to injection these attacks had occurred from two to four times a week with such violence that he was unable to perform his duties as a truck driver. During several weeks of hospital observation and bed rest his arterial pressure varied from 150/110 to 210/130, and he had an almost constant headache. Despite the chronic history, his retinal vessels were virtually normal, the heart was only slightly enlarged, and kidney function was intact. The urine was clear and intravenous urograms were negative. He refused operation but readily consented to injection.

Paravertebral alcoholic block was done on July 17, 1940. Before and during the procedure, his blood pressure ranged from 170/120 to 230/160. Five hours later it was 130/90; at twenty-four hours it was 140/95; at forty-eight hours 150/100. He walked out of the hospital on the third day with a reading of 160/110, complaining only of slight soreness in the back and stating that his head was unusually clear and comfortable.

Within a week the blood pressure had returned to its former level, the readings usually being in the neighborhood of 170/110. He resumed his work within a month, however, and from July, 1940, until November, 1941, he experienced only three or four abortive attacks, each lasting less than five minutes and extremely mild. For a few weeks after injection, he had a moderately uncomfortable neuritis on the left side of the trunk but he repeatedly expressed his delight over the results of the "treatment." We had expected the symptoms to recur in about six months and to recommend operation at that time but he remained in good health for nearly eighteen months. The patient himself noted that during this period of freedom from symptoms there was no visible sweating of his abdomen at any

time. During the latter part of the summer of 1941 he noted return of sweating, and symptoms recurred shortly thereafter.

In November, 1941, he had three severe attacks in quick succession and voluntarily requested another injection. At this time his physical examination had not changed perceptibly but the blood pressure was about 175/135. A sweat test revealed no areas of anhydrosis. On Nov. 22, 1941, he was reinjected as before except that this time the second lumbar segment was included on the right side. Again, there was a moderate but temporary drop in pressure for about twenty-four hours. Completeness of injection was proved by another sweat test (Fig. 1). He was back at work within a week with a pressure of 165/125 but stated that he felt very well.

On July 28, 1942, he reported that he had had only two mild attacks since his second injection. All visual difficulties had disappeared. He regarded himself as being at least "80 per cent improved." On the basis of these two experiences he was advised to submit to surgery.

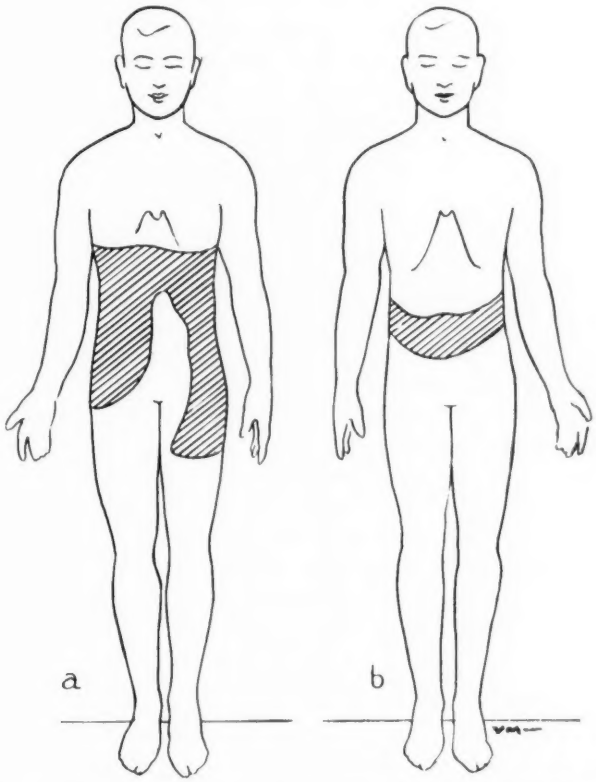


Fig. 1.—Areas of anhydrosis following paravertebral alcoholic block in (*a*) patient G. H. and (*b*) patient J. F.

CASE 2.—B. D., a 24-year-old white girl, for three years had experienced paroxysms of headache, palpitation, dyspnea, and flushing of the face four to six times monthly. Between attacks she felt perfectly well but had a persistent hypertension, the blood pressure fluctuating between 145/110 and 210/130. Her physical and laboratory examinations were negative except for questionable cardiac hypertrophy and minimal retinal sclerosis. During one such attack, her blood pressure was recorded as 180/130. She did not have paroxysmal tachycardia.

Paravertebral alcoholic block was done on July 18, 1940, without pain or difficulty. When she left the hospital forty-eight hours later, her blood pressure was 130/80. No neuritis developed. When next seen about six months later the arterial pressure had reached its preinjection level but she was symptomatically greatly improved. The paroxysms were far less frequent and severe, and she considered herself virtually well. No sweat test was done.

On Aug. 14, 1942, she reported that she had gone six more months without any symptoms whatever. More recently, the attacks had recurred in a very mild form and never oftener than once a month. Her physician stated that her blood pressure averaged about 160/115. She also was advised to submit to operation.

CASE 3.—J. F., a 44-year-old white physician, for three months had noted increasingly severe headaches, dimness of vision, exertional dyspnea, and precordial pain. Ophthalmoscopic examination revealed marked narrowing and tortuosity of the retinal arteries, arteriovenous compression of a high degree, a few scattered hemorrhages, and beginning papilledema but no exudates. The heart was moderately enlarged but there was no congestive failure. The urine contained small amounts of protein and a few casts. Urea clearance test was 50 per cent of normal; intravenous urograms, negative; spinal fluid pressure was 240 mm. water; initial arterial blood pressure, 215/140. No important drop occurred after three weeks of bed rest and thiocyanate administration, and the symptoms continued unabated. Visual acuity was so diminished that he was unable to read the newspaper or to sign his name.

On Oct. 4, 1941, the following segments were injected with procaine hydrochloride and alcohol: on the right side, the ninth, tenth, eleventh, and twelfth thoracic, and the first lumbar segments; on the left the first lumbar ganglion was omitted. For the next twenty-four hours his blood pressure varied between 155/60 and 170/90. He walked out of the hospital on Oct. 10, 1941, stating that he felt "like a different person." The headaches and vomiting had promptly subsided; he felt clearer mentally and was able to read without difficulty. Several observers thought the edges of the optic discs were more distinct. His blood pressure was 200/110. The area of anhydrosis is shown in Fig. 1.

In this instance, even the symptomatic improvement was short-lived. Within a month the cerebral complaints returned with such violence that he sought treatment elsewhere. Subdiaphragmatic splanchnicectomy was performed in November, 1941, with again temporary relief from headache. Blood pressure was essentially unaltered and he died on Jan. 25, 1942.

COMMENTS

We thoroughly agree with those who prefer operation to injection on the grounds of safety and certainty. If there were reliable means for predicting postoperative results, injection methods could have no defense. However, patients who are asked to undergo operation should be selected with all possible care. In cases where doubt exists concerning probable benefit from surgery, preliminary paravertebral alcohol injection may be of considerable prognostic value. Completeness of injection can be readily demonstrated by sweat tests. It remains to be seen whether there is consistent parallelism between the recurrence of symptoms and the disappearance of anhydrosis.

CONCLUSION

In three patients with hypertension, paravertebral alcoholic block has produced striking temporary symptomatic relief. It is suggested that the procedure be adopted as a method of preoperative selection of patients.

REFERENCES

1. Peet, M. M.: Splanchnic Section for Hypertension: a Preliminary Report, Univ. Hosp. Bull., Ann Arbor **1**: 17, 1935.
2. Peet, M. M., Woods, W. W., and Braden, S.: The Surgical Treatment of Hypertension. Results in 350 Consecutive Cases Treated by Bilateral Supradiaphragmatic Splanchnicectomy and Lower Dorsal Sympathetic Ganglionectomy, J. A. M. A. **115**: 1875, 1940.
3. Adson, A. W., Craig, W. McK., and Brown, G. E.: Surgery in Its Relation to Hypertension, Surg., Gynec. & Obst. **62**: 314, 1936.
4. Allen, E V., and Adson, A. W.: The Treatment of Hypertension; Medical Versus Surgical, Ann. Int. Med. **14**: 288, 1940.
5. Smithwick, R. H.: The Technic for Splanchnic Resection for Hypertension, SURGERY **7**: 1, 1940.
6. White, J. C.: Technic of Paravertebral Alcohol Injection: Methods and Safeguards in Its Use in the Treatment of Angina Pectoris, Surg., Gynec. & Obst. **71**: 334, 1940.

TRAUMATIC RUPTURE OF THE DUODENUM

With a Case Report

Jacob Sarnoff, M.D., and Benjamin H. Oremland, M.D.
Brooklyn, N. Y.

AMONG the many types of casualties in civil life and in the Armed Forces, crushing injuries of the abdominal viscera will demand our increasing attention, as the momentum and force of our war production and its execution are stepped up. This applies to those employed in the various industries, to those engaged in combat, and to civilians under air attack.

Solid organs, as well as hollow viscera, may be ruptured by the impact of external force. The liver, spleen, kidney, and pancreas may be ruptured by the direct crushng effect of an external object. A hollow viscus such as the bladder, stomach, or intestines either may be crushed, or may burst by the hydraulic pressure exerted on the distended organ[1] (Fig. 1). It was hydraulic pressure that was probably responsible for the rupture of the duodenum in the case to be reported.

Guibe,[2] in 1910, collected all the cases from the literature from 1835 to 1940 inclusive. There were 134 cases. In 17 of these, the rupture occurred at the duodenojejunal angle. Of these 17, 1 patient survived. In all, there were 62 operations with 4 recoveries. Eighty-four cases were collected from 1910 to 1940, with 37 recoveries. These improved results, no doubt, are in part due to the advances made in surgery during this period. Duodenal rupture occurred in about 10 per cent of all intestinal ruptures.

When one reasonably suspects such an injury, it is much safer to do an exploratory laparotomy, rather than procrastinate. One should not indulge in wishful thinking, hoping that the injury may be trivial and will require no surgical intervention. The high mortality in cases of duodenal rupture may be explained by: (1) the frequency of associated serious injuries, (2) operative delay, (3) nonrecognition of the rupture before or during the operation. The dangers of procrastination in intraabdominal injuries are mainly hemorrhage and peritonitis. The symptoms are those of shock due to hemorrhage or perforation.

During operation one may overlook a rupture of the duodenum if it occurs retroperitoneally. Emphysema and crepitation over the second and third portions of the duodenum, accompanied by a green spot or area overlying the rupture, are due to the extravasation of the duodenal secretion. These findings should put one on guard and make one search deeper for such an injury.

In a good many of the reported cases the condition was not recognized or treated until many hours or days after the accident. The

Received for publication, Feb. 17, 1943.

case to be presented illustrates some of the points discussed, as evidenced by the character of the accident, the operative findings, the clinical course and the end result.

CASE REPORT

History.—Nov. 26, 1942, at 1 P.M., M. M., a boy of 15 years, attempted to catch a fly ball during a baseball game. As he jumped for it, he ran into the tailboard of a parked truck. Bystanders said that the impact was so great that the truck actually moved when he struck it.

His abdomen struck the tailboard just below the costal margin and the boy collapsed. He then stood up and was taken to the family doctor's office by automobile. Examination at that time revealed a well-developed, muscular young man in great pain. Temperature was normal. The right side of the abdomen was tender, but no rigidity was present. There was no obliteration of liver dullness. A diagnosis of intra-abdominal injury was made and close observation advised.

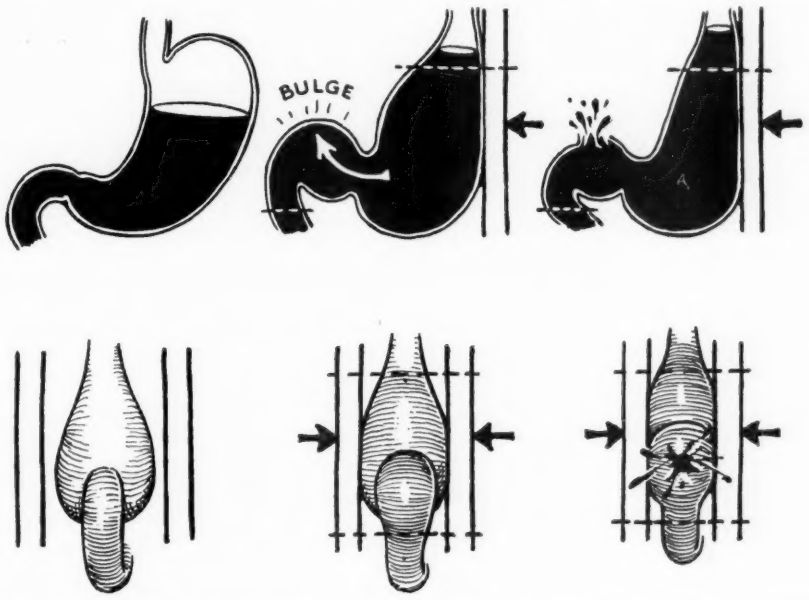


Fig. 1.—Mechanism of rupture of the duodenum by hydraulic force. A sudden blow to the abdomen may compress and block the contents of the stomach and duodenum causing it to burst by hydraulic pressure.

The drawing demonstrates diagrammatically the pressure on these organs as indicated by the arrows, and their blockage as indicated by the dotted lines.

The patient was taken home by automobile and put to bed. He vomited at 3 and 5 P.M. The vomitus was described as greenish black. The abdominal pain became more intense and the doctor was called again and saw him at 5:30 P.M. Examination then showed rigidity and marked tenderness on palpation, and rebound tenderness on the right side. Immediate hospitalization was advised. The patient was admitted to the hospital about 6:30 P.M. He was suffering from excruciating abdominal pain, more marked in the upper right quadrant. Pain was greatly aggravated by any motion. Examination showed the abdomen to be rigid and markedly tender. Immediate abdominal exploration was advised.

At 8 P.M. operation was performed by one of us (J. S.) under spinal anesthesia. A right rectus supraumbilical incision was made. On incising the periteneum, there was an escape of a moderate amount of greenish fluid from the peritoneal

cavity. The liver and spleen were palpated and were found free of injury. The gall bladder appeared normal. The gastrocolic and the gastrohepatic omenta in the region of the pylorus appeared infiltrated with bile-stained fluid, and were quite swollen and edematous. In attempting to pass through the anterior layer of the omentum, there was an escape of many gas bubbles and bile, suggestive of an injury to the duodenum or bile ducts. After penetrating and separating a good deal of the infiltrated gastrohepatic omentum, deep down, extraperitoneally, there was found a rupture of the second portion of the duodenum, probably just below the Ampulla of Vater. The opening extended transversely across the duodenum, involving about two-thirds of its circumference (Fig. 2). The edges were found

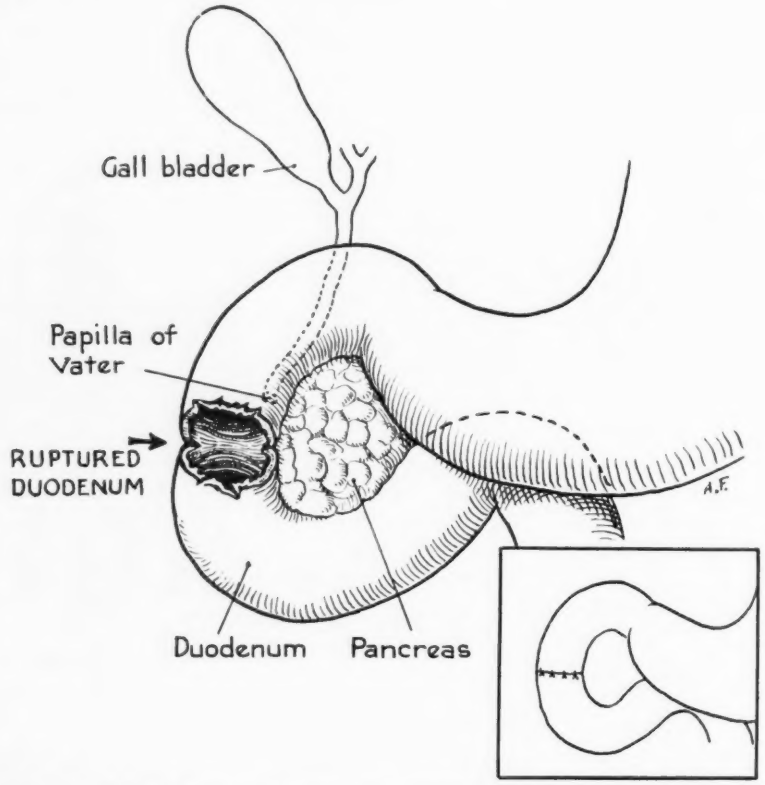


Fig. 2.—Rupture of the duodenum, just below the Papilla of Vater, involving about two-thirds of its circumference. The rupture was sutured in a transverse direction to avoid constriction of lumen, as shown in insert.

everted with the mucous membrane pouting. There was no bleeding, nor could any other injury be found. The head of the pancreas, adjoining the laceration, appeared normal and pinkish white in color, with no evidence of any trauma.

The fact that the pancreas and other adjoining structures were not in the least traumatized, led one to believe that the rupture of the duodenum in this case was due to hydraulic pressure (Fig. 1), and not to the direct crushing of the organ, although the duodenum is liable to be crushed because of its fixed position against the bodies of the vertebra. The fact that it is protected by the costal arch, liver, and floating intestines accounts for its less frequent injury. The muscles of the abdominal wall reflexly contract to protect the viscera from an oncom-

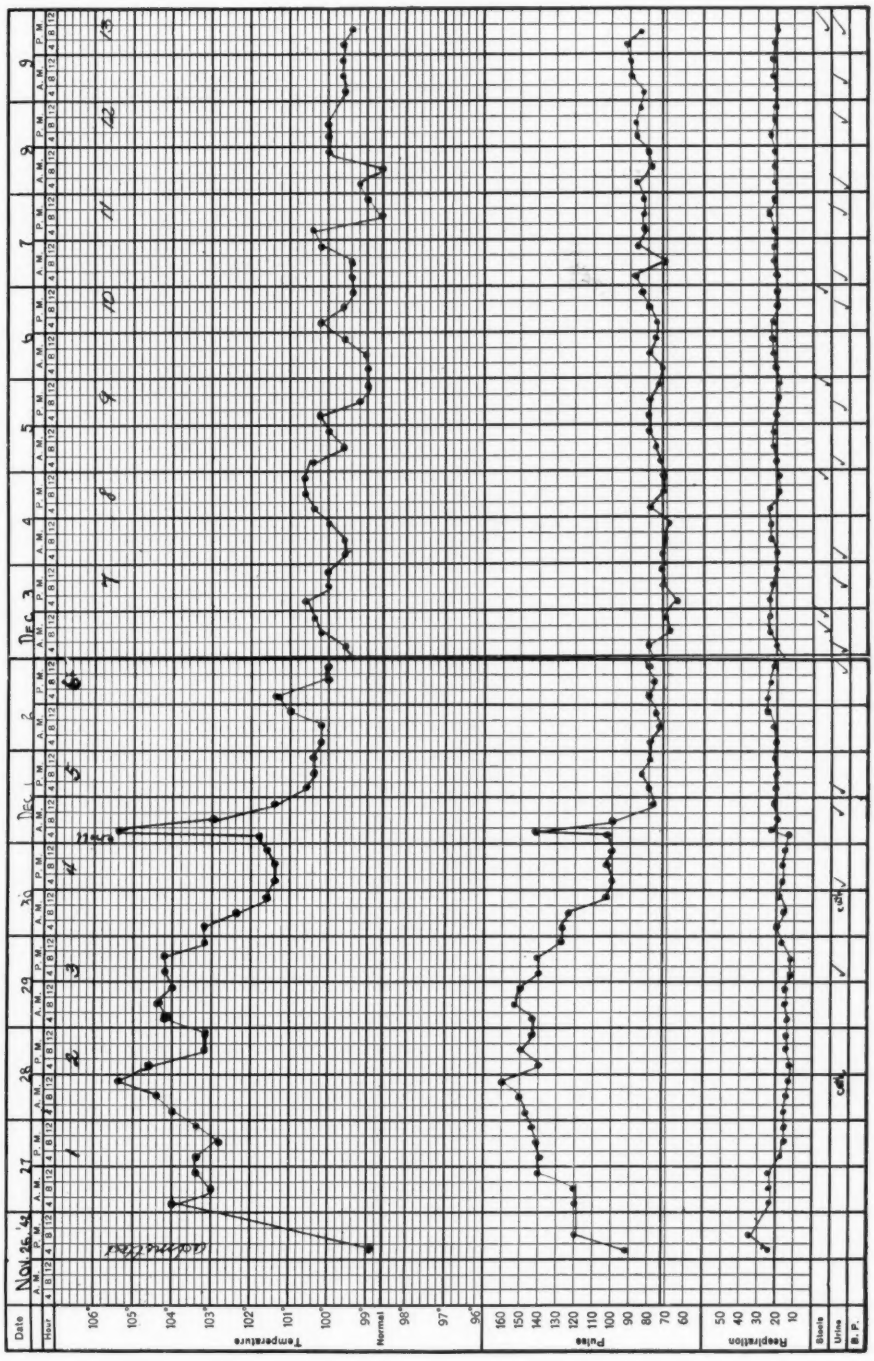


Fig. 3.—Graphic chart of the temperature, pulse, and respiration. The respirations were unusually slow, at about 20 per minute, in contrast to the rapid pulse reaching as high as 160, and high temperature topping 105° F. during the first week.

ing blow, when anticipated. The reason for the rupture of the duodenum may be partly explained by the fact that in this case the abdomen struck the tail end of the truck without the patient being aware of it as he concentrated his efforts on catching the ball. The abdominal muscles were momentarily relaxed, allowing the force of the blow to reach the duodenum.

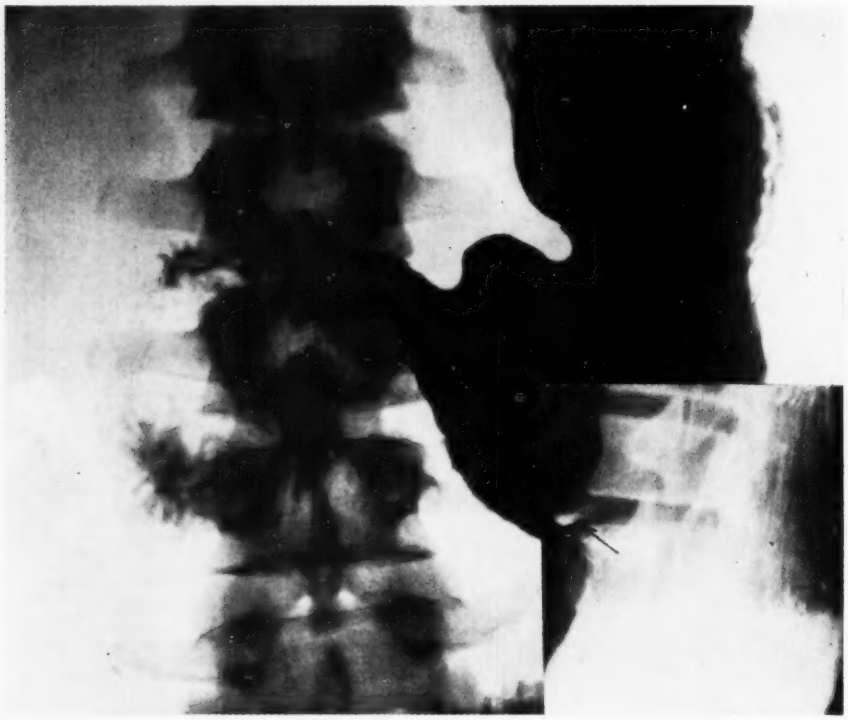


Fig. 4.—X-ray, Dec. 30, 1942, reveals no evidence of any pathology in the stomach or duodenum, except that there is a constant shelf or pocket (see insert) situated in the inner aspect of the duodenal curve which is at the site where the rupture was repaired.

The duodenum was closed transversely by interrupted 00 Lembert sutures, followed by a continuous seromuscular layer of sutures and a few interrupted sutures to reinforce the line of closure. Two cigarette drains were inserted toward the head of the pancreas, close to the line of anastomosis. Ten grams of sulfanilamide were introduced into the peritoneal cavity and the abdomen was closed in layers. A Levin tube was passed and 5 per cent glucose was administered intravenously.

About 4 A.M. or about eight hours after operation, the temperature rose to 104° F., pulse 120, respirations 22, and the patient became stuporous. On Nov. 28, the temperature rose to 105.4° F., pulse 160, respirations 12. The bladder was found to be markedly distended. The patient was catheterized and 25 ounces of urine were obtained. He was given 3000 c.c. of glucose intravenously, and a continuous Harris drip was started. The dressing was changed, moderate drainage found, and one Penrose drain removed. The condition of the patient grew worse; the pulse at times was imperceptible and respirations were 16 per minute (abnormally slow as compared to the rapid pulse and high temperature). Some crepitation was felt in the abdominal wall, a short distance away from the incision. This emphysema may have been an extension from the retroperitoneal site of the duodenal rupture, which

gradually came to the surface. The Levin tube drained bile-colored fluid. The patient was given a transfusion of 400 c.c. of whole blood, 10 c.c. of cortical extract were given intravenously, oxygen was administered, and 5 Gm. sodium sulfathiazole were given intravenously.

Nov. 29, the condition of the patient was poor, but better than the previous day. The temperature was 104.2° F., pulse 140, respirations 13 per minute. The abdomen continued to be soft, with no increased crepitation. Drainage from the Levin tube was less bile-stained and more clear; 10 per cent glucose was given intravenously, tea and water were given by mouth. Oxygen was continued, and cortical extract and 5 Gm. of sodium sulfathiazole were given intravenously.

Nov. 30, his condition took a marked turn for the better. The patient became rational and temperature was down to 101.4° F. in the afternoon. From then on, he continued to improve.

On Dec. 1, he had a chill with a rise of temperature to 105.2° F. which lasted a few hours. This chill was probably nonspecific in origin, and probably due to pyrogens in the intravenous fluids. The blood counts were as follows: On admission, 17,000 white cells and 76 polymorphonuclears. On Nov. 28, the red cells were 5,000,000, hemoglobin 82 per cent, white 14,600, and polymorphonuclears 72. On Nov. 30, red cells 4,150,000, hemoglobin 82 per cent, white 15,600, polymorphonuclears 72 per cent. The clinical course from Dec. 2, to date of discharge, Dec. 12, was uneventful. The temperature (Fig. 3) ranged from 100.5° to 98.5° F., the pulse and respirations were within the normal range. The drain was removed on the sixth day, and sutures were removed on the eighth day, with primary union, except at the site of drainage. The patient was discharged on the seventeenth postoperative day and when last seen, Dec. 29, 1942, was in good health. An x-ray checkup revealed no evidence of any obstruction at the site of injury (Fig. 4). The stomach contents passed freely through the duodenum as evidenced on fluoroscopy. There was slight retention of barium (a few cubic centimeters) at the site of the repair of the rupture.

SUMMARY

1. Rupture of the duodenum may not be recognized until some time after the injury.

2. Vomiting immediately after the injury is due to a reflex contraction of the pylorus with reverse peristalsis, a protective measure in cases of gastrointestinal involvement.

3. Injury to the duodenum may be overlooked during the operation especially if the rupture is extraperitoneal. The emphysema and greenish spots are clues which should lead us to search for such a perforation.

4. The stormy clinical course in this case: Hyperpyrexia, very rapid pulse, and unconsciousness for days, probably was due to the toxic absorption of the duodenal contents that seeped through retroperitoneally.

The introduction of sulfanilamide intraperitoneally and parenterally, together with blood transfusion, and intravenous glucose, intravenous cortical extract, and the administration of oxygen, no doubt were helpful supportive measures to tide the patient over the critical period.

REFERENCES

1. Robertson, Hugh: The Injured Abdomen, Am. J. Surg. **14**: 412, 1931.
2. Hinton, Drury: Rupture of the Duodenum by Blunt Trauma, J. Internat. Coll. Surgeons **3**: 485, 1940.

TRAUMATIC CHYLOTHORAX—A CASE TREATED WITH INTRAVENOUS CHYLE

EDWARD SCHNUG, M.D., AND JOSEPH RANSOHOFF, M.D.
CINCINNATI, OHIO
(From the Department of Surgery, College of Medicine of the University of Cincinnati, and the Cincinnati General Hospital)

THE treatment of chylothorax by intravenous injection of aspirated chest fluid has been carried out in eight reported cases to date. In 1908, Oeken[1] suggested this form of therapy and reported the first patient thus treated. The results in these cases are as follows: three recovered, three died, and two unchanged. The mortality recently reported by Scoville and Whitcomb[2] was apparently an anaphylactic death. One of the most carefully studied cases is that of Little, Harrison, and Blalock,[3] who observed this disease in a 17-year-old girl for almost two years, with the patient reported as alive but unimproved. They withdrew 550 liters of chylous pleural fluid and gave 23 liters intravenously during a six-month period. Nowak and Barton[4] recently reported a cure of spontaneous chylothorax after eight months by a phrenicotomy.

We wish to report briefly an additional case treated by intravenous administration of the aspirated fluid.

CASE REPORT

W. C., a 23-year-old Negro man, was admitted to the surgical service of the Cincinnati General Hospital shortly after having been shot in the right midclavicular line between the fifth and sixth ribs. He was vomiting and complaining of severe abdominal pain and pain over the dorsal spine. Physical examination revealed a normal man, not in shock, with a rigid, tender abdomen, and point tenderness over the eleventh dorsal vertebra. His white count was 16,000. X-rays showed a large caliber bullet to be lodged in the left posterior portion of the body of the eleventh dorsal vertebra.

Under cyclopropane anesthesia an exploratory laparotomy was performed. A small amount of blood in the peritoneal cavity was seen to have come from a half-centimeter wound in the upper right lobe of the liver. This wound was not bleeding. Although a complete exploration was performed, no other intra-abdominal injuries were found. Approximately 6 Gm. of sulfanilamide were placed in the abdominal cavity and the incision closed without drainage. The bullet wound was excised, cleansed, and closed.

The patient had a smooth postoperative course, taking water by mouth on the third day and an increasing diet thereafter. He received a course of sulfadiazine therapy totaling 54 Gm. over a period of nineteen days.

Received for publication, Jan. 8, 1943.

On the sixth postoperative day the patient developed moderate dyspnea. X-rays of the chest showed a massive right-sided accumulation of fluid and on the seventh day the first thoracentesis was performed. The culture of the fluid as well as that of all subsequent ones proved to be negative. The patient was placed on a fat-free, high protein diet. Following this, as shown on the accompanying chart, thirty-four taps were performed over a period of fifty days with a removal of 56,450 c.c. of chylous fluid. During an interval of twenty-seven days, 16,800 c.c. of this fluid were given to the patient intravenously according to the method described by Smith and Woliver[5] of this hospital. On occasions, slight chilly sensations formed the only systemic reaction to the injections; no significant change in pulse or blood pressure occurred.

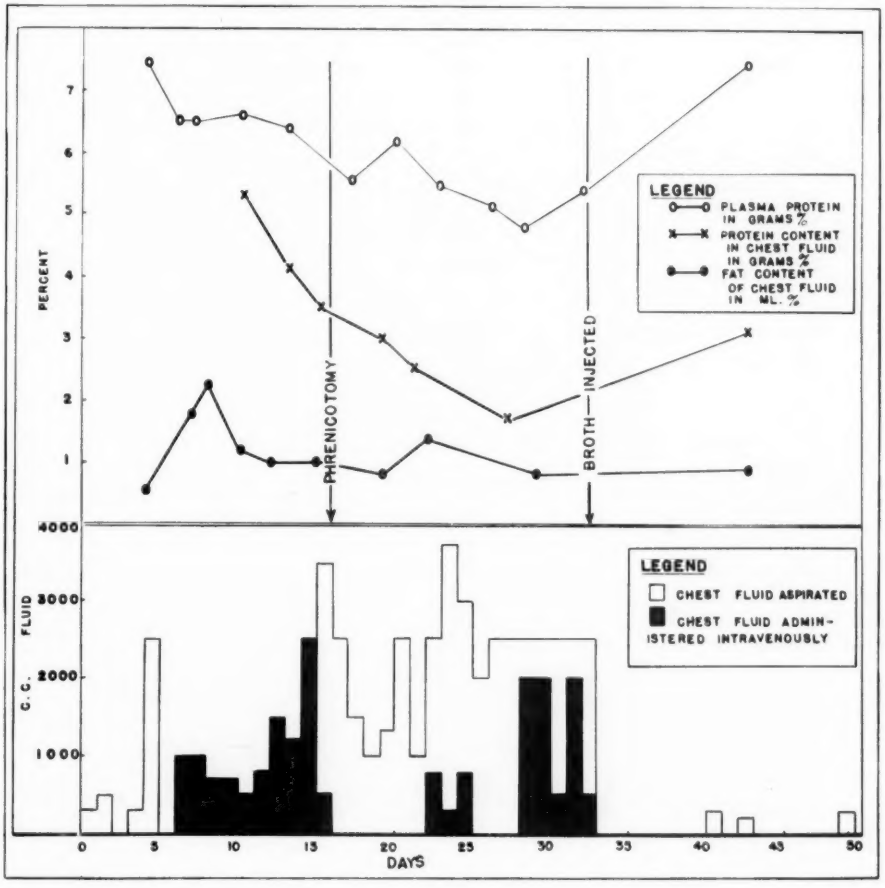


Fig. 1.

On the fifteenth day a right phrenicotomy was performed. Following this there was no apparent decrease in the rate of accumulation of fluid. From the sixteenth to the twenty-ninth days the intravenous therapy was very difficult to maintain because of a phlebothrombosis in all extremities. As can be seen from the chart, the patient's plasma proteins dropped steadily in spite of 1500 c.c. of blood plasma administered by hypodermoclysis.

On the twenty-ninth day and thereafter, at the suggestion of Louis G. Herrmann, heparin was used as an anticoagulant rather than sodium citrate. The heparin was

added in the ratio of 4 mg. to each liter of chest fluid. In the next five days it was possible to administer 7000 c.c. of chest fluid intravenously. The patient's plasma proteins rose towards normal levels (Fig. 1).

In spite of the patient's improved condition, there was no apparent decrease in the rate of collection of chylous fluid in the chest. It was therefore decided to inject 50 c.c. of sterile broth into the pleural cavity in order to stimulate a fibrinous reaction, as reported by Reinhoff,[6] and thus seal off the leaking duct. However, when attempting to aspirate as much fluid as possible before injecting the broth, only 2500 c.c. could be obtained. Previous to this date over 3500 c.c. had been withdrawn without the development of respiratory embarrassment. The broth was injected in spite of this sudden significant improvement. After the injection of the broth there was no leucocytic or temperature response to indicate a pleuritic reaction.

Following this day, there was apparently a complete cessation of leakage from the duct and small amounts of fluid were aspirated in order to hasten the re-expansion of the lung. The patient recovered completely.

DISCUSSION

This case demonstrates the efficacy of replacing the protein and fat lost into the chest cavity in chylothorax by intravenous administration of the aspirated chyle. In the interval between the sixteenth and twenty-ninth days, when there was a great disproportion between the amount of fluid withdrawn and that given intravenously, there occurred a precipitous drop in plasma proteins. Once this disproportion was wiped out, the plasma proteins again rose toward normal levels.

In spite of absence of untoward reactions in our patient, it is probably wise to take special precautions when first reinjecting the chylous fluid. A skin test with the fluid, as well as very slow injection of small amounts intravenously, should probably be carried out. It has also occurred to us that the size of the fat droplets may be important in the production of deleterious side effects.

The use of heparin as an anticoagulant in the fluid to be injected appears to be a valuable adjunct in the treatment of these patients. Blalock and co-workers[3] reported the extension of a pre-existing thrombophlebitis in their case on the administration of aspirated chyle. This complication was also the limiting factor in the intravenous replacement therapy in our patient until heparin was substituted for sodium citrate. The phlebothrombosis evoked by the fluid was then definitely decreased.

The injection of sterile broth or other fibrinogenic agents into the chest cavity may be of value in sealing off the leaking duct. It is unfortunate that in this instance the instillation of broth was carried out coincident with the apparently spontaneous cessation of the leak.

In our case neither diet nor phrenicotomy had any noticeable effect on the course of the disease. It is impossible, however, to predict what would have been the outcome here if these procedures had been omitted.

SUMMARY

The intravenous replacement of chylous fluid aspirated from the pleural cavity in cases of chylothorax represents a physiologic method of maintaining these patients. Energetic attempts toward these ends are indicated while other therapeutic measures are being carried out.

REFERENCES

1. Oeken: München. med. Wchnschr. **55**: 1182, 1908.
2. Scoville, W. B., and Whitcomb, B. B.: Arch. Surg. **45**: 747, 1942.
3. Little, J. M., Harrison, C., and Blalock, A.: SURGERY **12**: 392, 1942.
4. Nowak, S. J. G., and Barton, P. N.: J. Thoracic Surg. **10**: 628, 194
5. Woliver, E., and Smith, D.: Arch. Surg. **43**: 527, 1941.
6. Reinhoff, W.: Bull. Johns Hopkins Hosp. **53**: 390, 1933.

CARCINOMA OF THE PARATHYROID GLAND

KARL A. MEYER, M.D., F.A.C.S., AND ALEX B. RAGINS,* M.D.
CHICAGO, ILL.

(From the Surgical Service of Karl A. Meyer, the Department of Surgical Pathology, Cook County Hospital, and the Cook County Graduate School of Medicine, Chicago)

CARCINOMA of the parathyroid gland is rare. Although a number of cases have been reported,[1] the diagnosis of carcinoma of the parathyroid gland is questionable in view of the fact that the blood chemistry and x-ray examinations in these cases have been incomplete or have failed to show the characteristic changes. In some instances, however, one may concede the diagnosis of a carcinoma of the parathyroid gland, as reported by Petersma[2] and Sainton and Millot,[3] although no follow-up of their cases has been submitted in the literature.

Hall and Chaffin[4] have reported the autopsy findings on a case diagnosed as carcinoma of the parathyroid gland[1] which they have observed for six years. However, in view of their incomplete blood chemistry work-up and incomplete examination of the bones at autopsy, one hesitates to accept the final diagnosis of carcinoma of the parathyroid gland.

In a previous publication[1] we have had the opportunity to present a case of a diffuse fibrocystic disease of the bone due to a carcinoma of the parathyroid gland; the patient's response to surgical and medical management was reported. We would like to report now the complete clinical course of the patient and the post-mortem findings.

CASE REPORT

The following history is a brief abstract of the case up to September, 1938,[1] and the subsequent course of the disease until the patient's death on Dec. 24, 1940.

J. H., a white Greek man, was admitted to the Cook County Hospital on Oct. 8, 1937, at which time he presented clinical, laboratory, and x-ray findings diagnostic of hyperparathyroidism and diffuse fibrocystic disease of the bone (Table I and Fig. 1, *A*). In addition, calculi were observed in both renal pelves.

Following the extirpation of the tumor of the right parathyroid gland in October, 1937, there was a distinct relief from the subjective symptoms associated with a normal serum calcium and slight recalcification of bone. However, the relief from the subjective symptoms was temporary, and in March, 1938, the patient began to complain of recurring pain in the bones. In July, 1938, the patient had his right fifth finger amputated. At that time blood chemical analysis revealed a hypercalcemia and a hypophosphatemia, but the x-ray findings showed definite areas of recalcification in the bones (Fig. 1, *B*). At that time, too, a hard nodule about

*Major, Medical Corps, Army U. S., 297th General Hospital, Temple, Texas.
Received for publication, Dec. 31, 1942.

3 cm. in diameter was noted in the region of the right lobe of the thyroid fixed to the right jugular vein and carotid artery.

In view of the recurrent nodule fixed to the major blood vessels and failure of the patient to improve, he was readmitted to the hospital on Oct. 19, 1938, for further observation and x-ray therapy. He received approximately 3,000 r. through each of the three ports over the lateral and anterior aspect of the neck. He received weekly treatments of about 250 r. per treatment over a period of eight

A. *B.* *C.*

Fig. 1.—*A*, X-rays of the right radius and ulna showing the fibrocystic changes in the bone prior to surgical removal of the parathyroid tumor in the latter part of 1937. *B*, Eleven months postoperatively, showing tendency toward recalcification. *C*, Showing exaggerated fibrocystic changes of the right ulna and radius two years postoperatively, due to the persistent action of the recurring parathyroid carcinoma.

months. In addition, he received about 3,200 r. to his right wrist and both legs. The factors used were 200 KVP, 25 Ma., 50 and 62 cm. skin target distance, ½ mm. copper and 1 mm. aluminum filter, 0.9 e.cm. half value layer. The size of the ports was approximately 25 sq. cm.

Following the induction of x-ray therapy the patient left the hospital, only to return the following April, and for the last time in October, 1939. At this time a physical examination revealed a poorly nourished, poorly developed white man, who appeared ill. The blood pressure was 122/70; temperature, 98.6° F.; pulse, 76; respiration, 20. Teeth were in poor condition. The thyroid was not palpable, but

TABLE I

DATE	SERUM CALCIUM (MG. PER 100 C.C. N-9 TO 11)	SERUM PHOSPHORUS (MG. PER 100 C.C. N-3.5 TO 5)	PHOSPHATASE (BODANSKY UNITS)	VARIATION
10/21/37	16.1	3.1	22.0	Urea N., 21 Blood sugar, 75
10/26/37	15.1	3.0		Tumor removed
10/27/37	10.1			Calcium lactate, 30
11/11/37	8.0			gr. t.i.d.
11/18/37	9.1			
11/22/37	9.1	3.0		
11/27/37	9.1			Calcium lactate 10
12/ 8/37	9.0	2.4		gr. b.i.d.
6/ 8/38	12.9	1.99		
8/11/38	12.86	1.45	7.5	Pains return
11/18/38	15.05	2.05	7.8	N.P.N., 32
1/ 5/39	14.65	2.38	9.7	Total proteins, 7.9%
2/20/39	14.65	4.31	13.1	Total proteins, 7.2% Urea N., 27.5
10/23/39	13.66	3.13	27.6	
4/ 7/40	14.31	2.70		
6/13/40				Total proteins, 5.72%
11/14/40	13.70	10.00	40.0	

a hard, stony mass in the right side of the neck at its mid-portion and beneath the sternocleidomastoid muscle was palpable.

There was a marked deformity of the chest and the lower half of both anterior chest walls (Fig. 2). The left fifth to ninth ribs felt as if they were matted together. Expansion was poor bilaterally with distinct dullness over the lower half of the right and left chest wall posteriorly. Tactile fremitus and breath sounds were diminished over these areas.

The abdomen was scaphoid. The liver, kidneys, and spleen were not palpable. On rectal examination a small, hard nodule over the left lateral lobe of the prostate was palpated.

The left upper extremity showed a fracture through the left humerus and a marked fusiform swelling of the ulnar bone of the right forearm (Fig. 1, *C*). The right lower extremity revealed an almond-sized mass over the anterior upper third of the tibia, which was of a stony consistency. Beneath this was a soft mass involving the bones. The left leg showed an area of diffuse induration, swelling, and tenderness just below the knee joint. A distinct orange-sized mass in the medial side of the upper third of the tibia was also noted.

Blood chemistry analysis at the time of the last admission revealed a hypercalcemia, hypophosphatemia, and an increase in phosphatase (Table I). The patient was semiambulant and remained in the hospital. During his stay he fell while attempting to leave a wheel chair and sustained a fracture of the left tibia and fibula.

This fracture confined the patient to bed, where he remained up to the time of his death. While confined to bed he began to complain of pain in the left hip. A portable x-ray revealed a pathologic fracture of the left femur.

The condition of the patient became progressively worse and he developed generalized pain and moist râles in the chest. On Dec. 24, 1940, the patient died, approximately three years and eight months after the onset of illness.

The autopsy done by one of us (A. B. R.) revealed the following important autoptic findings.

External Findings.—The body was that of an emaciated white man. Over the neck was a healed surgical transverse scar measuring 12 cm. The right sternocleidomastoid muscle was more prominent than the left, and in the mid-portion an

irregular firm mass was palpated which seemed adherent to the underlying structures. The teeth were carious in the upper jaw and absent in the lower jaw. Both clavicles were prominent, the left being greater than the right, with a distinct bowing. The chest was deformed and there were numerous prominences beneath the skin, extending over all the ribs. The abdomen was retracted three fingerbreadths below the level of the chest. Finger tips were slightly cyanotic. The lower portion of the right ulna showed distinct bulging over the dorsal, lateral, and volar surface, measuring 7 by 3 by 5 cm. .The right little finger was missing (amputated

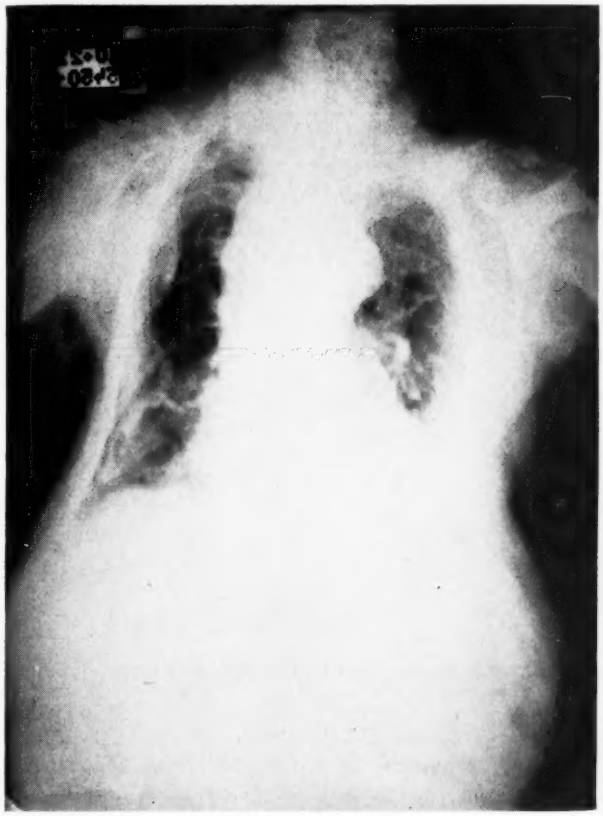


Fig. 2.—Chest x-ray showing extensive fibrocystic changes in the ribs and area of increased density of the lungs and marked deformity of the chest.

at the carpal-phalangeal joint). On twisting the right leg a distinct crepitus was elicited at about the middle of the right femur. A similar crepitus was elicited at the upper third of the left femur. On the medial aspect of the left knee was an ancient 5 cm. scar. Both tibiae showed irregular nodular processes extending above the surface of the bone. The skin over the legs was edematous, and on movement the crepitus feeling was elicited through the mid-portion of the left tibia. The skin over the legs was brown gray and edematous. The left leg was shorter than the right by 4 cm. In the right lower quadrant was an ancient healed 10 cm. herniotomy wound.

Internal Findings.—Lungs: The *right lung* was crepitant to subcrepitant throughout. The surface was smooth, light purple gray to pink gray and at the apex were small fibrous tags. The free surface lower lobe contained single nodes measuring from 2 to 4 mm. in diameter. The free surface of these nodes was light purple gray and extended buttonlike above the surface of the pleura (Fig. 3). On section

the node extended into the parenchyma for 3 mm., light purple gray mottled by opaque areas of gray white. The sectioned surface of the right lung was light purple gray. The mucosa of the bronchi was pale purple gray and smooth.

The *left lung* was dark purple gray, crepitant in the upper lobe and subcrepitant in the lower lobe. The surface was studded by nodes measuring from 0.4 to 2.5 cm. in diameter and pink tan gray in color (Fig. 3). On section these nodes were similar to those described in the right lung. The sectioned surface of the upper lobe was purple red and contained a small amount of frothy bloodstained fluid. The lower lobe was dark purple gray and contained small granular areas of consolidation. In the middle lobe the mucosa of the bronchi was purple red and covered by a small amount of bloodstained mucoid material. The mucosa of the trachea was pink gray, smooth and shiny.

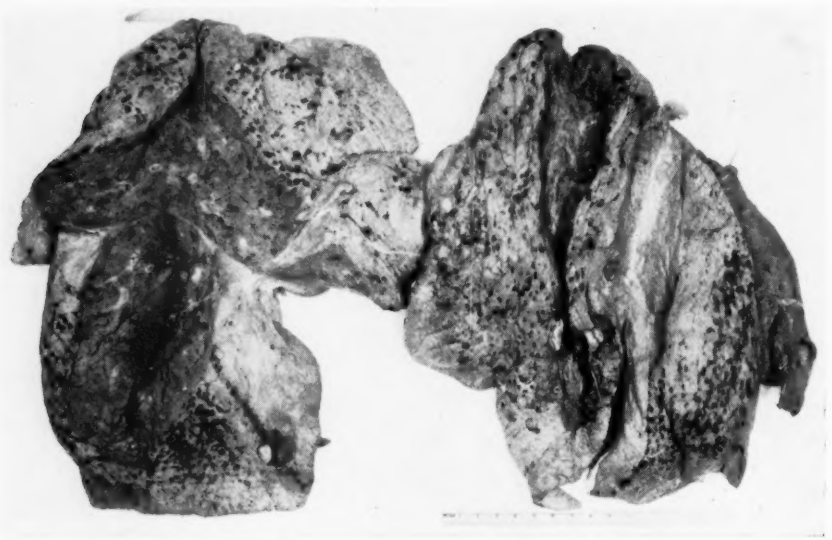


Fig. 3.—Lungs showing nodular buttonlike metastases of parathyroid tumor tissue of the pleural surfaces of the lungs.

Thyroid: The thyroid measured 5 by 3.5 by 1 cm. The left lobe was light purple gray tan. In the upper pole was a small oval-shaped nodule within the capsule measuring 4 by 3 by 1 mm. (Fig. 4, *D*). The left lobe of the thyroid measured 3 by 2 by 1 cm., was considerably firmer than the right, was purple gray, and on section was light pink gray.

Lymph Nodes: Adherent to the right jugular vein (Fig. 4, *B*) and compressing it from the posterior aspect was a firm mass measuring 3.5 by 2.5 by 2 cm. On section it was firm, gray white and in places distinctly calcified. The left subclavicular lymph node and peritracheal lymph node (Fig. 4, *C*) were enlarged up to 2 cm. On section this was light purple gray and in places centrally liquefied and partially calcified. The periaortic lymph node measured up to 2.5 cm.; on section it was purplish gray. The iliac lymph node measured up to 2.5 cm. and on section it was purple gray. The left iliac lymph node measured up to 1.5 cm. and was purple gray mottled by areas of red gray.

Kidneys: The kidneys, together, weighed 480 Gm. The *right kidney*, 180 Gm., measured 12 by 7.5 by 3.5 cm. The capsule stripped with ease. The surface was light purple gray, finely and coarsely gray. Over the convex surface of the kidney was a superficial depression 2 by 1.5 cm. and a darker brown gray. The cortex, up to 8 mm., was purple tan gray, with indistinct markings. The pelvis was slightly dilated; the upper calix was filled with small urinary concretions measuring

from pin point to 3 mm. in diameter. The lower and middle calix and pelvis were occupied by an irregular staghorn stone measuring 3 by 1.5 by 3.5 cm. In the lower pole of the kidney extending above the surface was a small gray white nodule, 4 mm., which extended into the parenchyma for a distance of 3 mm. (Fig. 5).

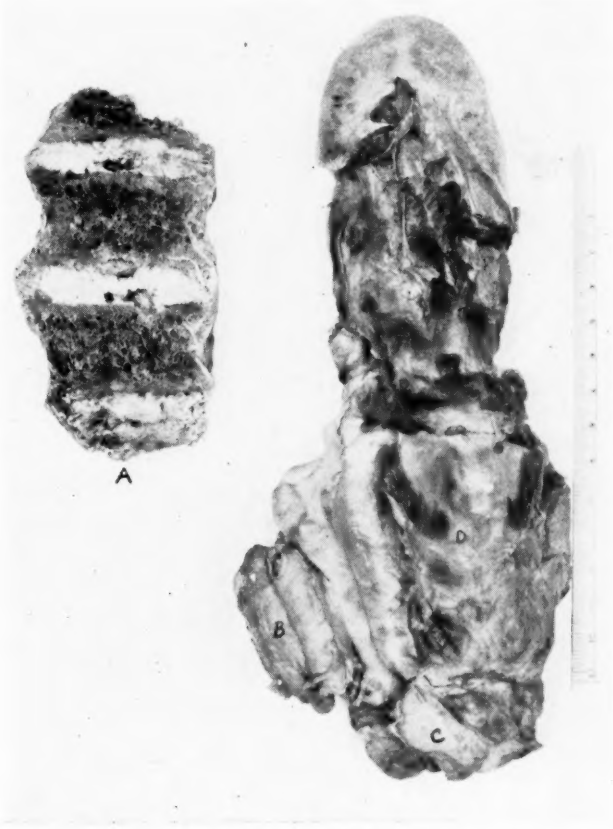


Fig. 4.—*A*, Showing the marked fibrocystic changes of the vertebrae. *B*, Perijugular lymph nodes contain tumor tissue with areas of calcification. *C*, Peritracheal lymph node showing metastases of tumor. *D*, Nodule in upper pole of lobe of thyroid showing invasion into the cricothyroid muscle.

The *left kidney* weighed 300 Gm. and measured 13.5 by 7 by 7 cm. The capsule was markedly adherent. The cortex in the upper pole was reduced to 1 mm., and the lower pole varied from 3 to 4 mm. The upper pelvis is markedly distended and filled by a creamy yellow purulent material (Fig. 5). The mucosa was pale purple gray, mottled by thicker areas of bright light yellow. The lower portion of the pelvis and its respective calices were occupied by a huge staghorn stone measuring 7 by 1.5 by 4.5 cm. and were brown gray and very firm. In addition, there were several facetted brown-gray stones with granular surface measuring 1 cm. in the greatest dimension.

The urinary bladder was filled by green-gray to yellow-gray urine. The mucosa was purple gray mottled by pin-point to 3 mm. sized vesicles filled with a slightly cloudy fluid and surrounded by a distinct brown-gray zone.

The prostate measured 4 by 5.5 by 4.5 cm. On section it was diffuse light purple, tan gray. In the right lateral lobe was a small irregular zone, 2 cm. in its greatest dimension, which was greenish gray.

Bones: All *ribs* were exceedingly fragile. These foci on section showed a soft red-gray medullary canal. There was a slight right-sided scoliosis of thoracic vertebrae, and practically all vertebrae, particularly the lumbar, show a marked thinning of cortex, and the medullary portion was composed of soft, purple-gray tissue (Fig. 3, *A*).

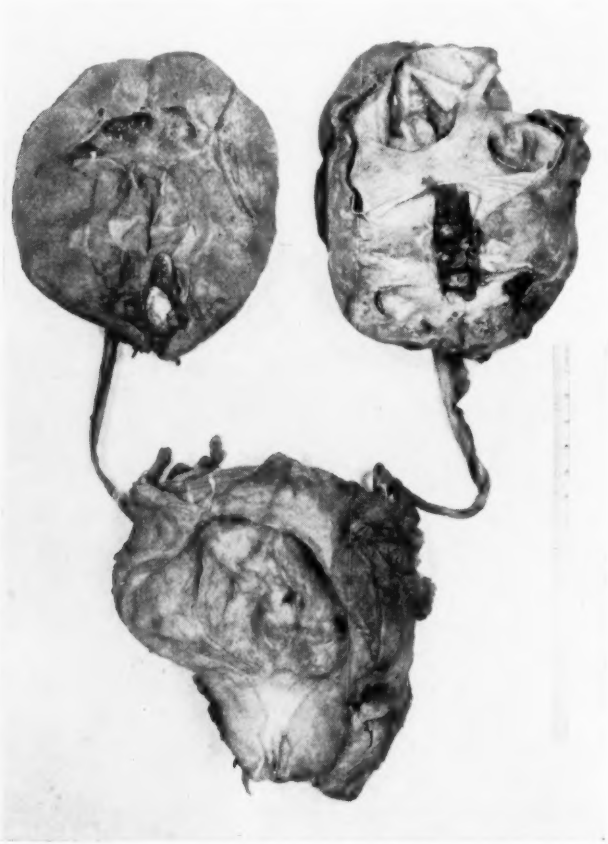


Fig. 5.—Showing bilateral renal calculi and a left-sided pyonephrosis of the left kidney and tumor metastases in the lower pole of right kidney as indicated by arrow.

The *right femur* showed a tremendous destruction of the cortex. The muscle tissue about the fracture area was infiltrated with blood. The cortex of the bone cut with very little resistance. The pelvic bone cut like butter, and the bone marrow cavity likewise was filled with purple-gray tissue.

The *left tibia*, at the site of fracture, showed a marked destruction of the cortex, the periosteum in this region was thickened and on scraping away left a roughly granular, yellow-gray to purple-gray surface. At the site of fracture the cortex was easily cut and the bone marrow appeared purple red. The lower third of the right ulna showed similar changes in the bone as described previously.

Practically the entire *sternum* was replaced by a soft, purple-red marrow mottled by areas of yellowish gray. The cortex in places was markedly thinned.

The spinous processes of thoracic and lumbar vertebrae were completely transformed into a reddish purple-gray mass.

The skull measured 18 by 14 cm.; the average thickness was 7 mm. The inner aspect was purple gray and granular. The bone was somewhat flexible and sawed

with ease. The sphenoid bone and the petrous portion of the temporal bone were purplish gray, and the consistency was markedly diminished.

Microscopic Examination.—Sections were made of all organs and the following are some of the pertinent findings.

Urinary Bladder: The transitional cell layer of the mucosa of the urinary bladder was markedly flattened and in places was missing. In some areas there was a slight downgrowth of the epithelial cells forming small nests of cells with oval-shaped nuclei and pale-staining vacuolated cytoplasm. Some of these nest cells were distinctly calcified. The submucosa was heavily infiltrated by round cells and plasma cells, and in places the submucosa was composed almost entirely of discrete nests of lymphocytes with single histiocytes filled with golden brown pigment and a few dilated blood vessels. The muscle bundles of the muscular layer were widely separated by edematous connective tissue and did not show any inflammatory changes.

Prostate: The *right lateral lobe* of the prostatic gland showed a moderate hypertrophy and hyperplasia of the epithelial cells lining the gland and in places showed papillary proliferations into the lumen which were filled and distended by numerous polymorphonuclear leucocytes. The fibromuscular stroma about these infected glands was infiltrated with lymphocytes, plasma cells, and polymorphonuclear leucocytes. In other areas the hyperplastic glands were not infected.

Kidney: In the *left kidney* many of the glomeruli were intact and of normal size. Others showed a slight to moderate thickening of Bowman's capsule. Still others, on the other hand, showed a partial to complete hyalinization of the glomerular tufts and glomeruli. The proximal and distal convoluted tubuli were dilated and in places filled with amorphous debris. The epithelial cells showed a slightly cloudy swelling and in places a moderate atrophy of the cell. Scattered throughout the cortex were small areas in which the tubules were widely separated by dense fibrous connective tissue proliferations which were occasionally infiltrated by round cells. The interstitial capillaries, arterioles, and venules were moderately dilated.

Throughout the section, both in the convoluted tubuli and in the collecting tubuli, were minute deposits of bluish-staining calcium material. Not infrequently, similar calcium deposits were seen in the interstitial connective tissue (Fig. 6, *B*). The epithelial lining in some of the collecting tubules was dissociated and filled the lumen. The larger blood vessels are slightly thickened.

The description of the *right kidney* was similar to that of the left, except for the fact that the small nodule described grossly in the lower pole of the kidney was composed of small nests and cords of cells containing large, irregular, hyperchromatic vesicular nuclei (Fig. 4, *C*). These nuclei were round to oval in shape. Occasionally, they were elongated and slightly indented. The chromatin granules were fairly coarse and in places appeared to be lodged on thin chromatin threads radiating toward the eccentric center of the nucleus where often a distinct nucleolus was discernible. The cell membrane was fairly distinct. The cytoplasm of most of the cells was pinkish staining and finely granular. Some cells possessed a clear nonstaining cytoplasm (Wasserhelle cells). The nuclei made up two-thirds of the diameter of the cell. These nests and cords of cells were widely separated by dense fibrous connective tissue strands which were slightly edematous and were continuous with a semiformed capsule separating the cortical renal parenchyma from the tumor nodule. However, within the capsule were single cords of the previously described cells. In the outer portion of the capsule were also present several atrophic tubuli.

Lungs: The tumor nodules found on the pleural surface of the lung as well as the one located beneath the pleura were composed of cords and nests of polygonal shaped large cells with round to oval-shaped vesicular nuclei (Fig. 6, *D*). Some of them stained rather deeply with hemalum. The cytoplasm of the greatest number of cells was pinkish staining and granular. Occasionally the cytoplasm was clear

and unstained, thus resembling water-clear cells. The cords and nests of cells were separated by thin fibrous connective tissue bands containing dilated capillaries filled with blood. The center of some of the cell nests were centrally necrotic, and occasionally a slightly atypical mitotic figure was seen. The tumor nodules in places appeared to be definitely surrounded by a thin connective tissue capsule which slightly compressed the adjacent alveolar structures of the lung. The alveolar

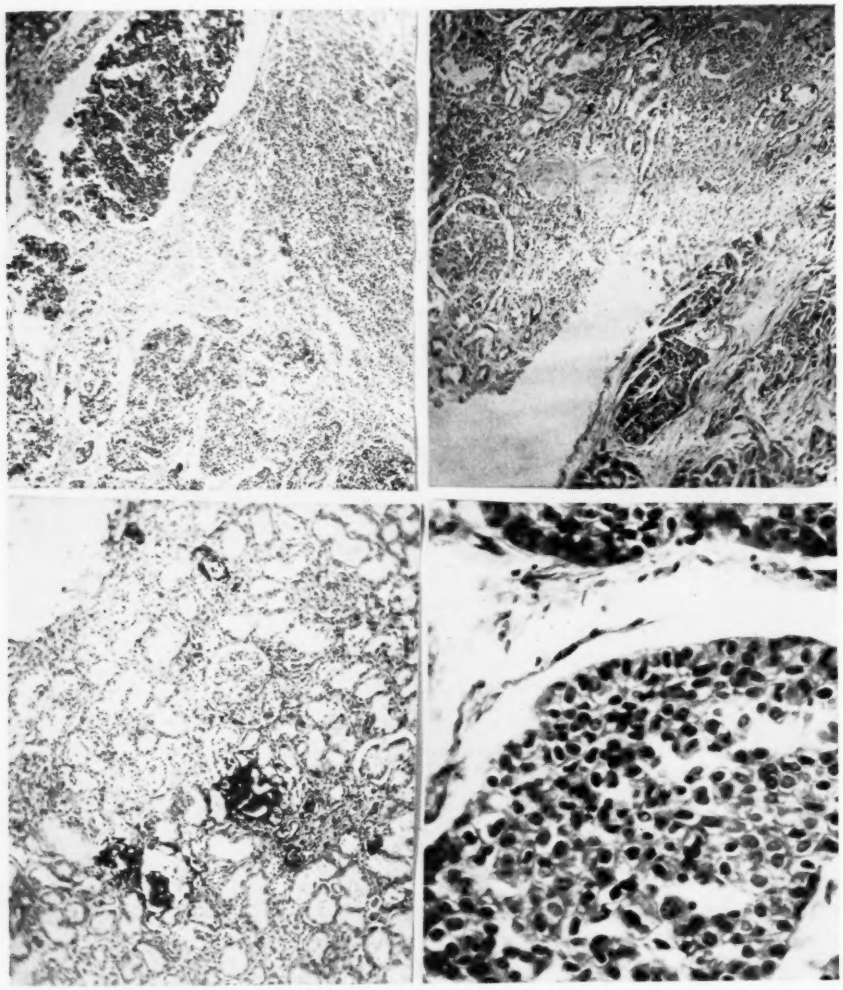


Fig. 6.—*A*, Metastasis of carcinoma of parathyroid to lymph node (magnification ×100). *B*, Nephrocalcinosis of kidney (magnification ×100). *C*, Metastasis of carcinoma of parathyroid to kidney (magnification ×100). *D*, Metastasis of carcinoma of parathyroid to lung (magnification ×440).

septal capillaries were slightly dilated. In places the small bronchioles were filled with desquamated epithelial cells and a few polymorphonuclear leucocytes. About the subpleural nodule the interstitial tissue in the region of the tumor metastases was widely thickened and infiltrated by polymorphonuclear leucocytes. In one area a large lymphatic vessel was obstructed by the tumor thrombus, as were some of the veins.

Lymph Nodes: The normal architecture of the *peritracheal* lymph node was altered, particularly at the periphery of the node, by large nests of tumor cells (Fig. 3, *A*) similar to those described in the lung. These tumor cells were in the

form of tumor thrombi filling the peripheral sinusoids and extending for a short distance into the cortical sinusoids. These cells were chiefly of the eosinophilic cell type. Occasionally a water-clear cell type was seen. The capillaries of the lymph node were dilated and filled with blood. The pulp was predominantly lymphocytic, although the sinusoids showed slight proliferation of the reticulum cells.

The periaortic, inguinal, and peripancreatic lymph nodes revealed a uniform picture characterized by lymphocytic hyperplasia of the germinal follicles which seemed to merge with the rest of the cortical and medullary stroma. The sinusoids appeared to be markedly dilated and filled by proliferated endothelial cells lining the sinusoids. The cytoplasm of many of the cells was vacuolated and the nuclei were eccentrically placed. In addition, a few polymorphonuclear leucocytes and eosinophiles were seen in the sinusoids. The trabeculae were thickened, as was the capsule of the lymph node.

The left retroclavicular lymph node was completely replaced by anastomosing cords and nests of polyhedral cells, most of them containing granular eosinophilic cytoplasm. Occasionally the cytoplasm of some of the cells was water-clear in character. The nuclei were large, round, oval, or elongated and distinctly vesicular. The chromatin was deeply staining and coarsely granular. These cells in places appeared to form rosettes in which the nuclei were markedly elongated and slightly lighter staining. Mitotic figures were seen but occasionally. These cords and nests of cells were surrounded by thick fibrous hyaline connective tissue bands in which were small nests of tumor cells, some of them lying within lymphatic spaces. In addition, there were scattered deposits of calcium, particularly about the blood vessels. The outer portion of the capsule of this mass was covered by fat. Between the anastomosing cords of tumor cells were thin-walled dilated blood vessels and focal extravasations of blood.

Left Parathyroid Gland: The left parathyroid gland revealed small nests of pale pink-staining cells with relatively ample cytoplasm surrounded by irregular nests of cells whose nuclei were markedly hyperchromatic and surrounded by small amounts of pale-staining cytoplasm with indistinct cell membranes and bands of fibrous connective tissue (Fig. 7, *C*).

Testicles: The left testicle showed marked atrophy of the seminiferous tubules. The cells for the most part were devoid of their nuclei and the cytoplasm of these was homogeneously pink staining. The interstitial tissue was small in amount and slightly edematous. In places there were small to large accumulations of Leydig cells, some of them containing a brownish pigment. The right testicle showed the seminiferous tubule in a somewhat better preserved state but definitely atrophic. In the interstitial tissue there were larger accumulations of Leydig's cells.

Hypophysis: The anterior lobe was composed of numerous eosinophilic cells arranged in small cords and occasional alveoli. In the alveoli were small accumulations of a pinkish blue-staining colloid. In the periphery of the anterior lobe and near the middle lobe there was a greater accumulation of basophilic and chromophobe cells which assumed an alveolar formation. The posterior lobe appeared normal histologically. The pars media contained few dilated cysts filled with a bluish material. There was no evidence of basophilic cell invasion of the pars posterior.

Adrenal: The cortex revealed that the cytoplasm of the reticular and fascicular layer cells was markedly vacuolated and relatively rich in lipoids, whereas the stratum granulosa cells had a homogeneous pink-staining cytoplasm. In one area there was a diffuse hyperplasia of the cortex. In this area the capillaries were slightly dilated. The medulla was composed of a normal number of large polygonal cells with dilated blood vessels.

Microscopic section of the thyrohyoid muscle revealed bundles of striated muscle which were superficially infiltrated by nests of tumor cells (Fig. 7, *D*) similar to

those described in the left retroclavicular mass. The major portion of the tumor mass, however, appeared to lie on the surface of the muscle.

The node about the jugular vein was composed of large nests of tumor cells similar to those described in the left retroclavicular mass. These nests were arranged in small anastomosing cords and were suggestive of small acini, some of them containing a pink-staining colloid material and others containing desquamated

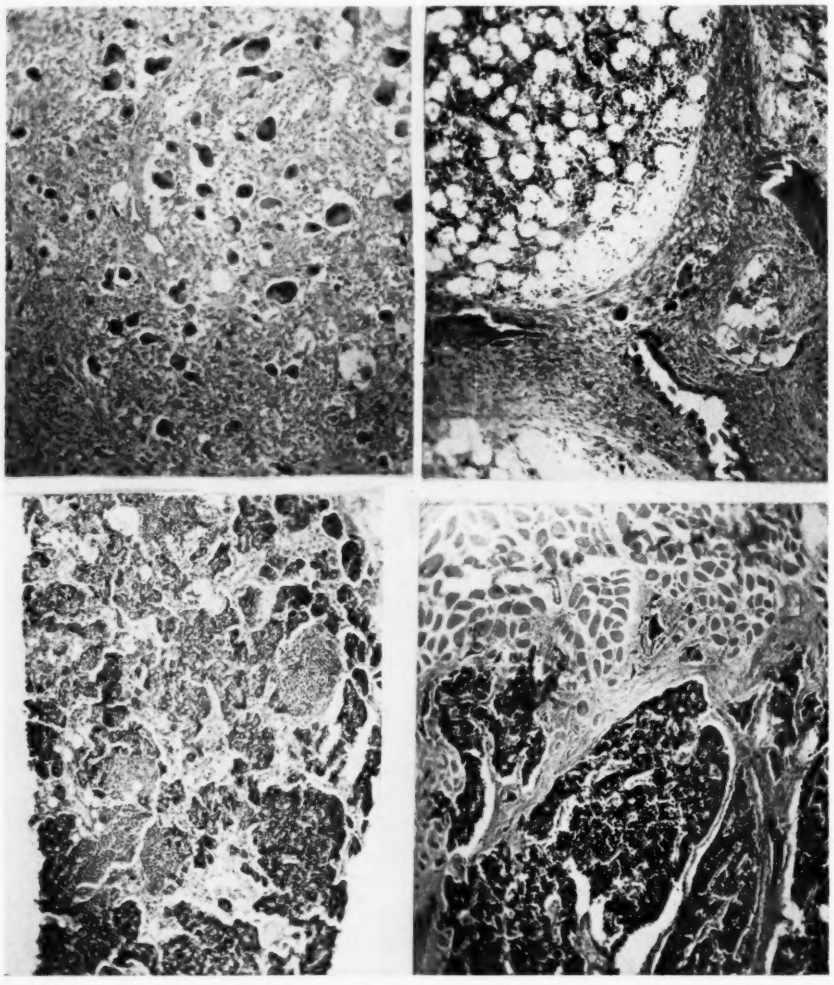


Fig. 7.—*A*, Spinous process of cervical vertebra showing severe fibrocystic changes of bone. *B*, Rib, showing active hematopoiesis and partial fibrocystic changes. *C*, Parathyroid gland from left side of neck showing nests of pale-staining eosinophilic cells. *D*, Infiltration of muscle tissue of neck adjacent to the cricoid bone.

tumor cells. These tumor cell nests were separated by wide bands of connective tissue, some of which were distinctly hyalinized. In other places the fibrous connective tissue bands contained small solid nests of tumor cells. Attached to the outer layers of the dense fibrous connective tissue were islands of fat which were infiltrated by small nests of tumor cells. Similar accumulations were seen about the blood vessels.

Bones: Sections of bone taken from the skull, temporal bone, middle and internal ear, right and left femur, right tibia, right ulna, ribs, skull, and spinous processes of the cervical vertebrae (Fig. 7, *A*) showed, for the most part, rather

uniform changes, except for the ribs, which will be described as to variations. The bone structures were replaced by a loose proliferating fibroblastic tissue which in places contained numerous giant cells, which, in turn, contained as many as fifteen to twenty oval-shaped, deeply staining, rather small nuclei. The chromatin of these nuclei was rather vesicular. The cytoplasm was rather homogeneous, deeply pink staining. Here and there were seen spicules of bone, some of them surrounded by large numbers of osteoblasts. Other spicules seemed to show atrophy and were surrounded by a few osteoclasts.

In the rib fibrosis of bone marrow spaces and atrophy of the bone were the predominating characteristics. Only a few scattered giant cells were seen. In the central portion of the rib there was still present active hematopoiesis (Fig. 7, *B*). The cortex of the bones was destroyed in all instances by the fibrous connective tissue proliferation. The stroma in all bones contained large focal areas of extravasations of blood. The petrosal portion of the temporal bone showed extensive rarification of the compact bone surrounding the cochlea. The giant cells in these areas of fibrosis lay adjacent to the bone spicules.

The final diagnosis reached then was recurrent carcinoma of the parathyroid gland, with metastases to the peritracheal, subclavian, and perijugular lymph nodes and to the lungs and right kidney; diffuse osteitis fibrosis cystica involving practically all the bones in the body; multiple pathologic fractures of the right and left femurs and the left tibia; bilateral nephrolithiasis, nephrocalcinoses; chronic ascending bilateral pyelonephritis and pyonephrosis of the left kidney, with severe atrophy of the parenchyma; chronic purulent cystitis and cystitis cystica; atrophy of the testicles with proliferation of the Leydig cells; marked edema of the leptomeninges; and cortical adenoma of the left adrenal gland.

DISCUSSION

The opportunity presented in doing a complete post-mortem examination in this unusual case proved that we were dealing with a malignant parathyroid tumor. In addition there were several other interesting findings which supported the clinical diagnosis.

The blood chemistry findings (Table I), although they showed a definite improvement in the blood calcium and phosphatase values, after a period of time (about 8 months after the removal of the tumor surgically) began to show higher values.

The blood phosphorus was almost always below the normal value, except for five weeks prior to the patient's death, when it rose to the unusual high of 10 mg. per 100 c.c. This finding was rather important in so far as it pointed to the fact that renal decompensation, independent of the previously existing malignant tumor of the parathyroid gland, had set in and had already induced a secondary parathyroid hyperplasia, as characterized by the slight enlargements of the parathyroid glands on the opposite sides with hyperplasia of the chief cells (Fig. 7, *C*). Johnson[5] reports similar findings in a case of a benign adenoma of the right lower parathyroid gland. In his case, however, hypertension associated with a severe arteriosclerosis presented itself, whereas in our case, despite the apparent renal decompensation, apparently due to nephrolithiasis associated with hydronephrosis, hypertension was not present.

It is interesting to note that Johnson,[5] as well as Brindle and Herman,[6] and Albright and Aub,[7] show calcification of the pyramids, and the two latter report of calcification in the cortex and medulla of the kidney. This calcification was demonstrated by x-ray visualization. Anderson[8] has demonstrated that in chronic hyperparathyroidism there are destructive microscopic changes in the kidney characterized by interstitial fibrosis, calcification, and infiltration by lymphocytes which lead to renal failure, and yet despite the marked renal failure the blood pressure need not necessarily be increased.

Calcification in the kidney was not the only site of calcification noted in our case. It was also observed in the metastatic lesion of the tumor to the lymph nodes, the thyroid, the urinary bladder, and the blood vessels of the heart. Although one must consider the x-ray irradiation as a possible cause of calcification following necrosis of tissue, we find evident support in the work of Bergstrand[9] that the calcification is part of the disease under discussion. In nine cases of primary (benign) hyperparathyroidism he found calcification in some of the tumors.

A factor which is quite important in the support of the diagnosis of the malignant tumor of the parathyroid gland is the marked progressive, diffuse, fibrocystic changes of the bones (Figs. 1 and 2). These are but single examples. Films taken ten days prior to the patient's death showed almost a complete destruction of the cortex of the bones. The marked fibrocystic changes are represented by the proliferating osteoclasts in the spinous process of the vertebrae (Fig. 6, *A* and *B*). Despite the extensive destruction of bone and bone marrow, the red blood cell count was rather constant, although terminally the hemoglobin was rather low. This may be explained on the basis that in the ribs there were still active foci of hematopoiesis and erythropoiesis (Fig. 6, *B*).

The predominating cell in our case resembled the chief cell, although the transitional cell and the water-clear cells were seen occasionally. This finding runs parallel with Castleman and Mallory's[10] observations in their report on benign adenomas of the parathyroid gland.

The effect of x-ray irradiation on primary hyperplasia of the parathyroid is still a moot question. Rappaport,[11] Huguet,[12] and Schnayer[13] report favorably on the therapeutic effect of x-ray irradiation in adenomas of the parathyroid and the associated bone changes.

Sainton and Millot[3] and Quick and Hunsberger[14, 15] are skeptical about the outcome of x-ray therapy, in so far as their patients failed to improve.

Our patient also failed to improve under rather extensive x-ray irradiation. However, we must be somewhat guarded in our opinion since we are dealing with a carcinoma of the parathyroid gland.

SUMMARY AND CONCLUSIONS

A case of carcinoma of the parathyroid gland with post-mortem findings is presented showing only a temporary improvement in the objec-

tive and subjective symptoms following extirpation of the tumor mass some twenty-six months before death. Eight months following the operation, the subjective symptoms reappeared, and a year later the fibrocystic changes of the bone became progressively worse, despite x-ray irradiation to tumor mass and bone. This was followed by a number of pathologic fractures. Six weeks before death the serum phosphorus rose to 10 mg., indicating renal decompensation.

The essential findings of the post-mortem examination were as follows: recurrent carcinoma of the parathyroid gland with metastasis to the peritracheal, subclavicular, and perijugular lymph nodes, the lungs, and the right kidney; generalized osteitis, fibrosis cystica of the bones; bilateral nephrolithiasis, bilateral chronic ascending pyelonephritis, left pyonephrosis with atrophy of the renal cortex and nephrocalcinosis.

REFERENCES

1. Meyer, K. A., Rosi, P. A., Ragins, A. B.: Carcinoma of the Parathyroid Gland, SURGERY **6**: 190-200, 1939.
   Hall, E. M., and Chaffin, L.: Malignant Tumor (Adenoma) of the Parathyroid Gland, West. J. Surg. **42**: 578, 1934.
   Guy, C. C.: Tumor of the Parathyroid Gland, Surg., Gynec. & Obst. **48**: 557, 1929.
2. Petersma, J. P.: Een Genal von Zickte von Recklinghausens (osteitis fibrosa cystica generalisata) met clinichse genezing na Verwizdering van een Maligna Adenoom von Byschildklier, Nederl. tijdschr. v. geneesk. **81**: 2225, 1937.
3. Sainton, P., and Millot, J. S.: Degenerescence maligne d'un adenome Parathyroidien eosinophile on cour d'un maladie de recklinghausen, Ann. d'anat. path. **10**: 813, 1933.
4. Hall, E. M., and Chaffin, L.: Final Report of a Case of Malignant Adenoma of the Parathyroid Gland, West. J. Surg. **48**: 685, 1940.
5. Johnson, J. W.: Primary Hyperthyroidism With Extensive Renal Calcification and Secondary Hyperplasia, Am. J. Path. **15**: 111, 1939.
6. Brindle, H. D., and Herman, N. G.: Diffuse Calcification Deposits Outlining the Kidney Lobules, Associated With Parathyroid Adenoma, Am. J. Roentgenol. **41**: 601, 1939.
7. Albright, F., and Aub, B.: Renal Lesions in Hyperparathyroidism, J. A. M. A. **102**: 1276, 1934.
8. Anderson, W. A. B.: The Renal Lesion in Hyperparathyroidism, Endocrinology **24**: 372, 1939.
9. Bergstrand, H.: Tumors of the Parathyroid Gland, Acta chir. Scandinav. **85**: 25, 1941.
10. Castleman, B., and Mallory, T.: The Pathology of the Parathyroid Gland in Hyperparathyroidism, Am. J. Path. **11**: 1-72, 1935.
11. Rappaport, F. G.: Contribution to the Study of Osteitis Fibrosa, Vestnik Khir. **16**: 271, 1929.
12. Huguet, E.: Un cas de maladie fibro-kystique de recklinghausen avec presentation de malade, Bull. et mém. Soc. de radiol. méd. de France **20**: 82, 1932.
13. Schnayer, J.: Ein Beitrag zum behandlung der osteitis fibrosa generalisata (Recklinghausen), Fortsch. a. d. geb. d. Röntgenstrahlen **36**: 1062, 1927.
14. Quick, A. J., and Hunsberger, A., Jr.: Hyperparathyroidism, Clinical Picture in Far Advanced Stages, J. A. M. A. **96**: 746, 1931.
15. Quick, A. J., Hunsberger, A., Jr., Eleason, E. L., and Hudson, N.: Hyperparathyroidism, Clinical Picture in Far Advanced Stages, J. A. M. A. **104**: 2248, 1935.

ARTERIOVENOUS FISTULA OF THE COMMON FEMORAL VESSELS WITH EXTREME DILATATION OF THE EXTERNAL ILIAC VEIN

Report of a Case

James R. Watson, M.D., and R. B. Miller, M.D.
Pittsburgh, Pa.

(From the Passavant Hospital and the John C. Oliver Memorial Research Fund of the St. Margarets Memorial Hospital, Pittsburgh)

INJURIES to the major blood vessels of the extremities, resulting in the formation of arteriovenous fistula, produce profound changes in the circulatory system. These changes are both structural and physiological and, while they involve both the arterial and the venous sides, the latter is the more adversely affected of the two, and is responsible for most of the signs and symptoms which characterize the disease.

The structural changes in the vein consist essentially of hypertrophy and dilatation. The hypertrophy involves the intima and media, at times giving it an appearance not unlike an artery, a change which had been referred to as "arterialization" of the vein. The dilatation may be diffuse and may extend for some distance proximal to the level of the fistula, or may be maximal locally at the site of the fistula, where it represents an almost constant finding. The degree of hypertrophy and dilatation varies considerably according to the size of the blood vessels involved and the size and duration of the fistula. The dilatation is also probably influenced by the resistance offered by adjacent structures, and would thus be apt to be less marked in an extremity, where the vein is surrounded by muscles and their fascial compartments, than in one of the body cavities where there is nothing more resistant than areolar tissue. In cases of arteriovenous fistula of the femoral vessels, the proximal dilatation has been frequently described as enormous, and Osler[1] demonstrated a case before the Johns Hopkins Medical Society in 1904, in which it extended for some distance proximal to the fistula and was sufficiently large to produce an abdominal tumor. The tumor's "origin was, however, not perfectly clear, and, so far as he knew, there were no other cases like this one in the literature." His case is reported as follows:

> The man—now 31 years of age—had, in his eleventh year, received a knife wound just above the right knee. This was soon followed by swelling of the calf of the leg and a little later pulsation was noticed along the femoral artery with the development of a swelling in that region. The patient's health had remained good and he was exceptionally vigorous except for some

Received for publication, Jan. 25, 1943.

disability in the right lower limb and for attacks of hemorrhage from varicose veins in the lower leg. Along the outer thigh reaching from the lower ribs to the foot, ran huge, tortuous varicose veins, and the whole right leg was enlarged. Thrombi were palpable in the veins, some of them organized and a few probably calcified. There was a pulsating swelling in Scarpa's space and along the femoral artery. Over this a thrill was felt most intensely about the middle of the thigh. In the abdomen was another pulsating tumor eight inches across and occupying most of the hypogastrium and right iliac fossa. The pulsation here, too, was expansile in character and over it a thrill could be feebly felt. The abdominal tumor was thought by Dr. Osler to be a large venous sinus associated with enormous venous dilatation above a traumatic arteriovenous aneurysm.

The occasional occurrence of a true aneurysm of the artery above the level of an arteriovenous fistula, led Reid[2] to believe that the abdominal tumor noted by Osler was probably an aneurysm of the iliac artery rather than a venous dilatation. The following case is evidence of the fact that such extreme venous dilatation can occur, although it must be quite uncommon.

W. H., a Negro man, 49 years of age, was admitted to the Passavant Hospital in January, 1942, for treatment of an arteriovenous fistula of the right femoral vessels and a mass in the right lower abdominal quadrant. He had been shot in the posterolateral aspect of the right thigh eighteen years before, the bullet traversing the thigh and lodging just beneath the skin about three inches below the medial aspect of Poupart's ligament. There had apparently been very little bleeding at the time, and after a brief and uneventful recovery, he returned to work as a janitor, with no residual other than a slight amount of swelling of the right leg and the presence of a purring sensation in the groin. He had no other signs or symptoms until two years before admission when he began to have dyspnea on exertion and occasional attacks of precordial pain with radiation to both shoulders, which gradually increased in severity until he was forced to give up his work. Six months before admission, he noticed for the first time a painless swelling in the right lower abdominal quadrant which slowly increased in size until it reached the size of a grapefruit, and coincident with this there was marked increase in the size of the right leg with the appearance of varicosities and ulcers. The past medical history was essentially negative.

The positive findings on physical examination were limited entirely to the cardiovascular system. The heart was enlarged in all directions, with the maximal apex impulse in the sixth left intercostal space in the anterior axillary line. There was a systolic murmur which was best heard over the apex and which was transmitted to the left axilla and the right sternal border. There was a large mass in the right lower abdominal quadrant, which measured 14 by 10 by 7 cm. (Fig. 1). The right leg was much larger than the left, there being 15 cm. difference in circumference at the mid-thigh and 7 cm. at the mid-calf. There were varicosities and pigmentation, and in the region of the ankle there were two scars of healed varicose ulcers. There was a constant thrill and bruit over the right groin just below Poupart's ligament, the bruit being transmitted to the abdominal mass. The popliteal and dorsalis pedis vessels were not palpable.

Obliteration of the fistula by digital pressure produced a drop in the radial pulse rate from eighty-eight to sixty-six beats per minute, and caused the abdominal mass to disappear, giving the clinical impression that it was a saccular dilatation of the external iliac vein. With the collapse of the mass a large, somewhat tortuous external iliac artery could be outlined just lateral to it.

Repeated urinalyses were negative except for a slight trace of albumen. The blood count showed 4,220,000 red blood cells per cubic millimeter of blood, with 87 per cent hemoglobin and 10,300 white blood cells. The differential count was normal. The nonprotein nitrogen was thirty-six and the creatinine 1.6 mg. per 100 c.c. of blood. The Kolmer and Kahn tests were negative. A cystogram (Fig. 2), made to determine the size and position of the abdominal tumor, showed the bladder to be displaced toward the left side by a large mass which occupied the right half of the pelvis. The mass appeared to extend several centimeters above the superior border of the bladder.

Fig. 1.

Fig. 2.

Fig. 1.—Illustration showing the location of the abdominal mass and the marked enlargement of the involved leg.

Fig. 2.—Cystogram showing the deformity and displacement of the bladder produced by the dilated iliac vein.

The patient was kept in bed with the right leg elevated for a week in an unsuccessful attempt to decrease the edema.

Operation was performed on January 10, under local anesthesia. A vertical incision was made over the common femoral vessels below Poupart's ligament. Many dilated and tortuous veins were immediately encountered in the subcutaneous tissue. These were divided and the incision gradually deepened to expose the fistula. Poupart's ligament was not divided as we did not want to expose the venous mass in the pelvis. The fistula was found to be about 5 cm. below Poupart's ligament and was embedded in dense fibrous tissue with the anterior femoral cutaneous branch of the femoral nerve intimately adherent to it on its lateral aspect. The artery and vein above the fistula were each approximately 4 cm. in diameter, although measurement of the vein was inaccurate as part of it lay beneath the artery. There was some sclerosis of the artery. The wall of the vein was thickened, although it was not as thick as that of the artery. The vessels below the level of the aneurysm were small, the artery measuring 1 cm. in diameter while the vein was even smaller. There were several large arterial and venous

branches entering the fistula, for the most part on its posterior aspect. The artery could not be separated from the vein above the level of the fistula, so an attempt was made to free them en masse from the underlying tissue. They were quite adherent and, in spite of careful dissection, the vein ruptured, resulting in a sudden and profuse hemorrhage. Large packs were immediately inserted in the wound and firm pressure was applied. Nitrous oxide and oxygen anesthesia was started in order to expedite the control of the bleeding. A vertical incision was made just above Poupart's ligament and the ligament was divided over the course of the vessels. The external iliac artery and vein were separated and freed without difficulty where they passed over the anterior ramus of the pubis, and were tied using umbilical tape. The large saccular dilatation of the external iliac vein was readily visible at the upper angle of the incision (Fig. 3) and was seen to collapse when the vein was tied. The incision above the ligament was closed using fine silk, and the repair of the fistula continued under local anesthesia.

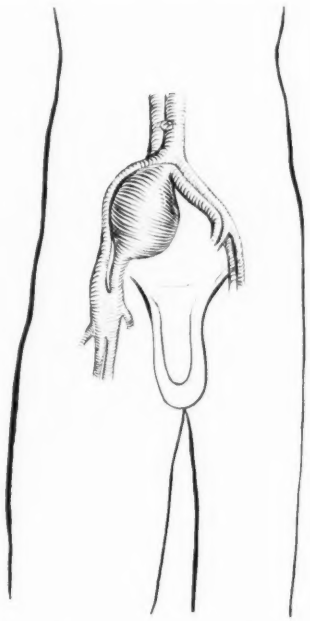


Fig. 3.—Diagrammatic sketch of the relationship between the arteriovenous fistula and the saccular dilatation of the iliac vein.

The packs were removed from the lower incision and the wound was found to be dry. A tape was then passed beneath the artery and vein below the fistula and tied, it also being impossible to separate them here for separate ligation. In view of the difficulties already encountered in attempting to separate the vessels from the underlying tissue above the level of the fistula, it did not seem advisable to attempt it again even though such a course meant abandoning removal of the fistula. Several sutures of No. 2 silk were passed around the vessels at the level of the fistula and tied in an effort to obliterate it in this manner. Although the vessels tended to fill slowly between the sutures, auscultation with a sterile stethoscope failed to reveal a bruit and there was no palpable thrill. The wound was thoroughly irrigated with sterile normal salt solution and closed in layers with fine silk. The operation required four and one-half hours. In spite of the hemorrhage the pulse was steady between ninety and one hundred beats per minute throughout the operation, there being no evident drop when the vessels were tied or the fistula sutured. The blood pressure, which was 175 mm. of mercury systolic and 80 mm.

diastolic at the beginning of the operation, was 145 and 120 mm., respectively, at the end.

The patient made an uneventful recovery and left the hospital twenty-two days after operation with both incisions healed. The improvement noted was dramatic. The heaving sensation which had been present in his chest before operation had entirely disappeared. The heart was quieter and the murmur was only faintly audible. The systolic and diastolic blood pressures were maintained at their post-operative levels and were 140 mm. of mercury systolic and 110 mm. diastolic at the time of dismissal. The most pronounced change was in the size of the heart, the transverse diameter decreasing from 20.3 cm. before operation to 16.6 cm. eighteen days after operation. Electrocardiographic studies made before and after operation showed only a right axis deviation, with no essential alteration after operation other than a decrease in the pulse rate. The tissues of the leg were not as tense as they had been and measurements showed a decrease of 3 cm. in circumference at the calf and thigh. The mass in the right lower abdomen reappeared during the first few days after operation and gradually returned to its original size. It possessed a firmness, however, which had not been present before. The only disquieting feature, and this was not entirely unexpected in view of the fact that the fistula had not been removed, was the reappearance of a faint thrill and bruit over the operative area on the fifteenth day.

The discharge note stated that "A thrill and bruit are still present over the femoral triangle, although they are not nearly as loud as they had been before operation. The abdominal tumor is as large as it was originally, but is now firm and not compressible, and does not decrease in size when pressure is made over the site of the arteriovenous fistula. It is apparently filled with blood clot and should gradually decrease in size as the clot organizes. The patient will have to be watched closely and if the heart shows any tendency to enlarge, another operation on the fistula will be necessary. The patient has been advised to spend most of his time at home and in bed for the next two months, and to avoid all exertion."

When last seen, six months after operation, he had no complaint other than cramping pain in the calf of the right leg after walking for a distance of a block and a half. It was readily relieved by a brief period of rest and he was contemplating returning to his job. There had been a slow but progressive decrease in size of the leg, there being now only 5 cm. difference in the circumference of the two thighs. The thrill and bruit were scarcely discernible over the femoral triangle. The abdominal mass was firm and was decreasing in size. The artery lateral to it was also firm and less distinct and, according to the patient, had suddenly stopped pulsating about three weeks previous. The heart was quiet and regular in rhythm, and on x-ray examination was found to have decreased another 0.8 cm. in its transverse diameter. Branham's brachycardic sign was negative, pressure over the fistula producing no decrease in the pulse rate of ninety-two beats per minute. It is still too early to predict a complete cure, although so far the result has been entirely satisfactory.

DISCUSSION

For anatomic reasons it is difficult to determine the extent and degree of dilatation of the vein proximal to an arteriovenous fistula of the common femoral vessels. It is quite possible that saccular dilatation of the external iliac vein can occur and still not be of sufficient size to be apparent. The vein, regardless of the degree of dilatation at the level of the fistula, is necessarily decreased in size where it passes beneath Poupart's ligament, and is then apt to become dilated above it where

the retroperitoneal tissues do not offer any resistance. The studies of Reid and McGuire,[3] which demonstrated the tremendous increase in blood volume in the proximal vein, cause one to wonder why the dilatation is usually not more marked. The extreme dilatation of the external iliac vein found in the case described appears to be unusual, and with the exception of the case reported by Osler, we have been unable to find any similar reports in the literature. The venous origin of the abdominal tumor is beyond dispute in view of the fact that it was necessary to expose it at its lower margin through a misadventure during the operation. It apparently represents a late complication for, according to the patient's history, it occurred seventeen and one-half years after the inception of the fistula. Although there is no mention of the duration of the abdominal tumor in Osler's case, the fistula had been present for twenty years. In our case it was interesting to observe the collapse of the abdominal tumor when the fistula was obliterated by digital compression, and we offer this test as a method to differentiate between tumors of arterial and venous origin which occur proximal to an arteriovenous fistula.

SUMMARY

1. A case of arteriovenous fistula of the common femoral vessels is reported in which there was a saccular dilatation of the external iliac vein of sufficient size to produce an abdominal tumor.

2. A diagnostic sign is described which will permit a clinical differentiation between a venous dilatation and an arterial aneurysm occurring proximal to an arteriovenous fistula.

REFERENCES

1. Osler, Wm.: A Case of Arteriovenous Aneurysm, Johns Hopkins Hosp. Bull. **16**: 146, 1905.
2. Reid, Mont R.: Abnormal Arteriovenous Communications, Acquired and Congenital. III. The Effects of Abnormal Arteriovenous Communications on the Heart, Blood Vessels and Other Structures, Arch. Surg. **11**: 25-42, 1925.
3. Reid, Mont R., and McGuire, Johnson: Arteriovenous Aneurysm, Ann. Surg. **108**: 643-690, 1938.

LEG ULCERS AS A COMPLICATION OF CAISSON DISEASE

S. Thomas Glasser, M.D., F.A.C.S., New York, N. Y.

(From the Department of Surgery, New York Medical College, Flower and Fifth Avenue Hospitals and Metropolitan Hospital; Louis Rene Kaufman, M.D., F.A.C.S., director, New York)

CAISSON disease presents a great variety of symptoms inherent upon the generalized pathology. However, the complications are surprisingly limited chiefly to the bones and joints. Our presentation of a case of caisson disease complicated by leg ulcers is prompted following a careful search of the literature which failed to reveal this complication.

Caisson disease classified in various texts[1-2] under the heading of high barometric pressure is also known as: aeropathy; compressed-air illness; divers' paralysis; divers' palsy; the bends. The present war makes this disease of particular interest because of its association with deep-sea diving, bridge building and other related work. It is also of importance because the knowledge obtained in studying this disease has been of inestimable value in aviation medicine. Exposures to high pressure occur in bell, caisson, diving suits, and tunnels.

The pathologic physiology is extremely interesting. It must be remembered that the disease is not attributable to anoxia as supposed by those unfamiliar with this entity, but is the result of the return from high atmospheric pressure. In other words, high pressures are well tolerated but the ill effects are evidenced when the individual returns to atmospheric pressure. When this occurs, the nitrogen, which had been forced into solution in the plasma and tissues, will be released. Under increased pressure, the component gases of the air go into fluid solution after passing from the pulmonary alveoli to the circulation. This solution is in direct proportion to the partial pressures (Dalton's Law) of the air's components, nitrogen and oxygen. The two gases must be distinguished because nitrogen is an inert gas which is not utilized by the body and tends to free itself when the external pressure is lowered. On the other hand, oxygen is readily utilized by the hemoglogin and body tissues. Of further importance is the fact that nitrogen is not absorbed equally by the various tissues. Consequently, the degree of pressure and the time it is exerted determine the amount of nitrogen absorbed by the individual tissues. The same applies to the subsequent lowering of pressure when the nitrogen is eventually expelled in the alveoli. Tissues which have a comparatively poor blood supply are slower in their absorption of nitrogen, but when saturated, take up greater amounts than well-vascularized tissue. Fat absorbs five times

Received for publication, Feb. 18, 1943.

as much as water. This absorptive capacity is also elevated in ligaments, bones, spinal white matter, liver, and spleen. Following tissue saturation, a sudden release in pressure results in "bubbling." These numerous bubbles or gas emboli account for the multiplicity of symptoms. The possibilities for damage as a result of these numerous gas emboli are numerous, and depend upon the initial degree of saturation and the speed of the return to normal pressure. Thus, obstruction to circulation, rhexis, and tissue pressure are the basic sources of the ensuing symptoms. If the individual is returned to normal atmospheric pressure gradually, body equilibrium takes place by slow release of nitrogen and emboli formation is obviated.

The symptomatology must necessarily be strange and varied because of the extensive involvement of tissues. Improper decompression, or lack of it, will affect the patient accordingly. The onset of symptoms is immediate in severe cases but generally averages one hour. Death may ensue shortly after return to atmospheric pressure and is attributable to pulmonary, cardiac, or cerebral involvement. This applies particularly to obese individuals. An excellent description and classification of the symptoms is that of Behnke,[3] namely, bends, chokes, and paralysis. The bends are most common, consisting of pains in the extremities and joints. Abdominal cramps accompanied by nausea and vomiting are also common. The unyielding tissues of the extremities, particularly in the joints, account for the pain. In chokes, involvement of the pulmonary vessels is responsible for the asphyxia picture which is often associated with bloody frothy expectoration. Paralysis is less common than bends and is a grave sign. Here the pathology lies chiefly in the central nervous system. Paresis, paraplegia, and hemiplegia are rare findings.

Briefly, the treatment consists of recompression to the original high level followed by decompression in stages and reduction of previous pressures by one-half. This method has proved more efficacious than a steady gradual decompression. Helium-oxygen mixtures (80 and 20 per cent) have been found to be a valuable adjunct in the decompression. Helium, an inert gas, is one-seventh as dense as nitrogen and is less readily put into solution while its diffusibility is greater and thus more readily freed from solution.

The following case report presents a new complication in caisson disease, namely, leg ulcers.

CASE REPORT

J. C. (No. 131523) was admitted June 23, 1941 and discharged Dec. 30, 1941. The patient, a former caisson worker, aged 58 years, was admitted to the Metropolitan Hospital with a chief complaint of multiple leg ulcers of about four years' duration. The ulcerations were preceded by the appearance of multiple bullae on both legs. After a few days, the blisters broke down and the resulting ulcerations have persisted up to the present time. The patient states that his knees have been "stiff" for about six years. He had had several attacks of the "bends." Both legs had felt slightly numb for many years.

On examination, the patient appeared well developed and in no apparent distress. Except for the local condition, the physical findings were normal. There was marked melanotic pigmentation of both lower extremities. The absence of varicosities and swelling was noted. The pedal, popliteal, and femoral pulses were readily palpable. Ulcerations of the legs consisted of many small ulcers and several large ones on the lower one-third of both legs. The ulcers appeared indolent, were moderately demarcated, and were covered by fairly healthy granulations and a small amount of seropurulent discharge. The edges were neither undermined nor indurated, and there was only little evidence of fibrosis at the bases. The anterior thigh muscles were rigid on palpation and the knees showed limitation of movement (about 50 per cent), evidently due to partial ankylosis.

During the subsequent course of treatment, wet dressings, adhesive strapping, and Unna boots, no improvement resulted. On Aug. 16, 1941, many of the ulcers were "seed" grafted with the thigh as a donor site. Unna boots were again applied. On Sept. 29, 1941, further grafting was performed using Thiersch grafts. The "takes" following both operations were only about 50 per cent successful. Although the ulcers were kept clean and bed rest maintained, healing remained refractory. Unna boots were applied on Dec. 30, 1941, and the patient was discharged to the outpatient department. Follow-up examination revealed only slight improvement. In Feb., 1943, the patient was in a hospital for chronic diseases and the ulcers remained about the same as on discharge from the Metropolitan Hospital.

DISCUSSION

The formation of ulcers is probably attributable to ischemia. Behnke's investigations showed that gas bubbles could be seen only in the vessels. He states, "Supporting the vascular ischemia origin of bends is the fact that application of pressure promptly relieves symptoms. This response might not be anticipated were the injury due to extravascular bubble formation which would imply cellular destruction." The only reference to skin manifestations in the literature is that of Mellinghoff.[4] His patient was admitted with evidence of peripheral circulatory collapse and some symptoms of the "chokes." Most interesting was the "marble" appearance of the extremities in which the pale blue areas of skin turned to a dark blue color. The marmoration of the skin was accentuated on coughing (Valsalva test). These blue spots had sharp outlines. Marmoration disappeared in a few days and no residual signs remained. The author explains the marmoration by the capillary stasis due to the increasing size of nitrogen bubbles which block capillaries. The stasis in the capillaries clears up when the nitrogen is carried away. The marmoration is apparently more marked with peripheral circulatory collapse and this stasis starts a vicious cycle with added circulatory collapse due to stasis. It is surprising to me that with these marmoration phenomena, in the more acute cases, more instances of breakdown in the skin do not occur. In my case, the probability of local thrombosis and extravasation of blood into the skin and neighboring tissues may be the cause of the subsequent ulceration. Thorne,[5] in his study based on 300 cases, made the observation that "the appearance of mottling and blotching with subcutaneous hemorrhages is further evidence denoting large amounts of free gas

in the circulation.'' In this author's large experience the only cutaneous manifestations noted were ''pruritus, erythema, purplish mottling and blotching.'' This occurred in only 20 of the 300 cases. Most observers agree that skin manifestations are early or impending signs of caisson disease. By analogy, one might expect skin ulceration for the same reason that damage to the central nervous system with paralysis results from pressure necrosis. We cannot account for the apparent rarity (no reports in the literature) of skin breakdown and ulcer formation except by the fact that the skin is elastic and pliable. In discussing the complications of caisson disease, Thorne notes that ''the complications of caisson disease are limited to the bones and joints. The symptoms of onset are insidious and are delayed from six months to a year or more following repeated attacks of the disease.''

A consideration of the differential diagnosis is pertinent in this discussion. Varicose and arteriosclerotic ulcers are definitely ruled out by the aforementioned findings. Against the type of multiple ulcerations seen in erythrocyanosis frigida is the absence of evidence of vasospastic phenomena and the patient's sex. The question arises as to whether the ulcers are of the postphlebitic variety. This diagnosis is not tenable in the absence of a history suggestive of previous phlebitis, the painless character of the ulcers, the absence of straight hard palpable veins, the absence of induration and dermatophytosis.

SUMMARY

A case of chronic leg ulcers as a complication of caisson disease is described. This complication is not mentioned in the literature and must be considered as an exceptionally rare finding.

REFERENCES

1. Meakins, J. C.: Practice of Medicine, Ed. 3, St. Louis, 1940, The C. V. Mosby Company, pp. 1339-1340.
2. Best, C. H., and Taylor, N. B.: Physiological Basis of Medical Practice, Ed. 2, Baltimore, 1939, Williams & Wilkins Company, pp. 579-580.
3. War Medicine—A symposium: New York Philosophical Library, 1942, Lt. Com. A. R. Behnke, Jr., M.C., U. S. Navy, pp. 4, 6, 7.
4. Mellinghoff, K.: Skin Manifestations in Caisson Disease, Ztschr. f. klin. Med. **127**: 457, 1934.
5. Thorne, E. J.: Caisson Disease: A Study Based on Three Hundred Cases Observed at the Queens Midtown Tunnel Project, 1938, J. A. M. A. **117**: 585, 1941.

A NEW SIMPLE AND RAPID METHOD FOR HERNIAL SAC LIGATION

ROBERT LICH, JR., M.D., M.S.,* AND RALPH B. SAMSON, M.D.†
PITTSBURGH, PA.

(From the Department of Surgery of the United States Marine Hospital)

THE various operations and modifications of operations for the repair of hernia are virtually limitless and it seems almost beyond the realm of possibility to offer another which would be wholly original. However, it is not our purpose to advocate another method of herniorrhaphy, but indeed to offer an original simple and rapid procedure, applicable to all, which will reduce the time of hernial sac ligation from minutes to a mere matter of seconds.

Some two years ago Robert D. Mansfield‡ and one of us (R. L.) experimented with several original methods in order to effect hernial sac closure both more quickly and easily. Several methods were developed and though seemingly of value, none demonstrated the desired attributes of simplicity, speed, and positive closure in every instance. The present idea, though conceived at that time, was later put in use and proved so amazingly simple, rapid, and absolute that we are reporting our experience.

The hernial sac is exposed in the conventional way and the redundant tissue extracted so that the neck is well isolated. The sac is then maintained under tension and a Furniss clamp applied across the point of desired ligation (Fig. 1). Vision within the sac is necessarily maintained so that no intestinal loop or omental tag is caught in the jaws of the clamp. After the clamp is closed and tightened, a needle threaded with the suture (No. 8 spool cotton in our work) is inserted between the jaws of the clamp and certainty is made that the needle penetrates the entire breadth of the now corrugated hernial sac. It is important that tension be maintained on the redundant sac until the needle is in place. The distal portion of the sac is now excised with a scalpel, the clamp removed, and the suture pulled into position and tied. This will effect a very tight purse-string closure of any peritoneal sac irrespective of its fragility and width provided it can be placed within the jaws of the Furniss clamp. Also, it is to be noted that only a negligible amount of tissue remains above the point of ligation so that only a minimum of

*Chief of Surgery, P. A. Surgeon (R), U. S. Public Health Service.
†Assistant Surgeon (R), U. S. Public Health Service.
‡Major R. D. Mansfield, Medical Corps, U. S. Army.
Received for publication, March 17, 1943.

devitalized tissue remains following sac closure. As stated earlier, the use of the Furniss clamp in hernioplasty will reduce the operative time by several minutes and converts an oftentimes troublesome technical and retractive labor into an incidental step of the operative procedure.

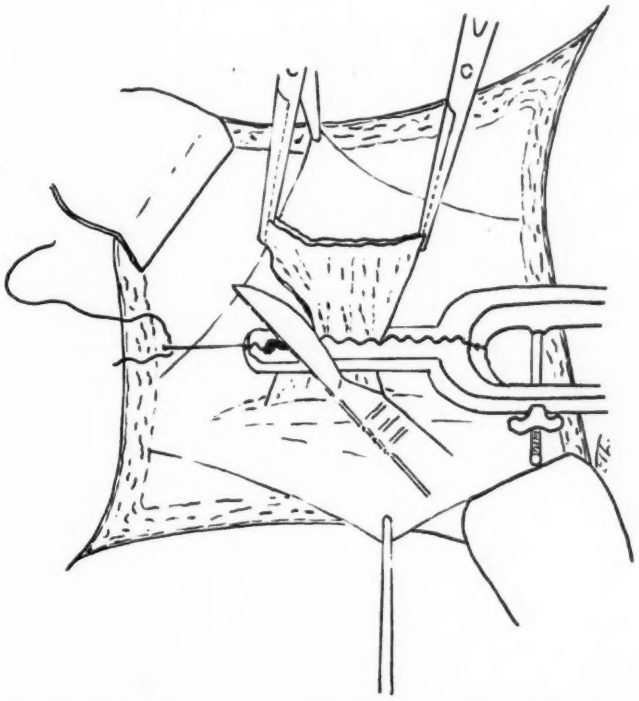


Fig. 1.—Furniss-Clute clamp applied, with needle in place and amputation of hernial sac in progress.

SUMMARY

A new, simple, rapid, and positive method for hernial sac closure is outlined employing the Furniss clamp, originally advocated for intestinal anastomosis, which will prove its value to the surgeon following a single trial.

Erratum

On page 946 of the June, 1943, issue in the article "Resection of the Colon in Six Cases of Hirschsprung's Disease" by Louise Yeazell, M.D., and H. Glenn Bell, M.D., San Francisco, Calif., the dosage mentioned at the end of the fifth line should read "syntropan 0.05 Gm. twice a day."

Recent Advances in Surgery

Conducted by Alfred Blalock, M.D.

SULFONAMIDES IN SURGERY

Victor Richards, M.D., San Francisco, Calif.
(From The Department of Surgery, Stanford University School of Medicine)

ALTHOUGH the sulfonamide group of drugs has been known to organic chemists for more than thirty years, it first achieved clinical importance in 1935, when Domagk[1] showed experimentally that prontosil was effective in combating streptococcal infections in mice. Since 1935, more than 1,300 sulfonamide compounds have been studied but few of these have endured clinically. It was soon discovered that sulfanilamide was not effective in treating staphylococcal and pneumococcal infections, and research with these organisms led to the development of sulfapyridine, in 1938, by Whitby,[2] and of its more soluble sodium salt, in 1939, by Marshall and Long.[3] Frequently, sulfapyridine produced nausea and vomiting, and it proved no more effective against staphylococcal and pneumococcal infections than sulfathiazole, which was introduced a year later by Fosbinder and Walter,[4] and by Lott and Bergeim.[5] In 1940, Roblin, Williams, Winnick, and English[6] presented sulfadiazine as a still less toxic and equally active drug in combating pneumococcal, streptococcal, staphylococcal, and Friedlander organisms. Sulfadiazine has proved to be the drug of choice for systemic administration against these organisms.[7] In 1940, Marshall and co-workers[8] offered sulfaguanidine in an effort to produce intestinal antisepsis, and now this drug is being supplanted for this purpose by succinylsulfathiazole (or sulfasuxidine) following recent studies of Poth and Firor.[9] That sulfanilamide is both safe and effective when introduced locally into wounds was demonstrated, in 1939, by Jensen, Johnsrud, and Nelson,[10] who employed the drug in the management of compound fractures in civilians.

Chemistry and Pharmacology.—All of the sulfonamide drugs are white, odorless, and nearly tasteless. The sodium salts are soluble, alkaline (hydrogen-ion concentration 8 to 10), and unstable to heat. One per cent solution of sodium sulfapyridine has a hydrogen-ion concentration of 10.1, sodium sulfathiazole 9.4, and sodium sulfadiazine 8.7.[11] The essential chemical structure of the group is a benzene ring with an amino group in the para position with respect to the sulfonamide

or sulfonamide-derivative radical. The amino group must be in the para position. The solubilities of the various compounds are clinically important and are as follows for water at 37.0° C. in milligrams per 100 cubic centimeters: sulfanilamide 1,400, sulfapyridine 49.5, sulfathiazole 94, and sulfadiazine 12.3.[11] The sodium salts of sulfathiazole and sulfadiazine are soluble up to 5 per cent and are suitable for intravenous administration when dissolved in sterile distilled water. The solubility of sulfanilamide and sulfapyridine is the same in urine as in water, but sulfathiazole is soluble up to 230 mg. per 100 c.c., and sulfadiazine up to 60 mg. per 100 c.c., particularly if the urine is slightly alkaline. Acetylsulfadiazine is even more soluble than sulfadiazine in urine.

The sulfonamide drugs are harmless to the body tissues in therapeutic doses, but bacteriostatic to the organisms against which they are effective, thereby distinguishing them as chemotherapeutic agents. They are absorbed readily by any channel, the peak of intestinal absorption being at four to six hours. Sulfadiazine is absorbed more readily and constantly than sulfathiazole, permitting an easier control of an effective blood concentration. Following absorption these drugs remain in the blood for a variable time depending upon the rate of absorption, the degree of acetylation, and the rate of excretion. Again, sulfadiazine is excreted less rapidly than sulfathiazole. Sulfapyridine is absorbed and excreted erratically. Large doses of these drugs, particularly sulfanilamide, lead to methemoglobinemia with a lowering of the oxygen saturation of the blood, but sulfanilamide is the only one producing acidosis. All of them have some direct antipyretic effect which is most marked with sulfapyridine. These drugs, once absorbed, are distributed relatively uniformly in all body tissues, the concentration being lowest in the skin, brain, bone, and fat. Sulfathiazole yields a low concentration in normal spinal fluid but filters readily through inflamed meninges.

It is well recognized that sulfathiazole and sulfadiazine are much more soluble in biologic fluids than in water. The hydrogen-ion concentration of blood is 7.5, and at this concentration sulfathiazole is 83.4 per cent ionized in the form of salt, and sulfadiazine 92.9 per cent. Sulfathiazole and sulfadiazine are, therefore, probably transported in the blood chiefly in the form of sodium salts.[11]

A physiologic attempt at detoxification occurs by acetylation of the para-amino group, probably in the liver. The acetyl compounds are therapeutically inactive. Acetylation is greatest for sulfapyridine (45 to 75 per cent), less for sulfanilamide and sulfathiazole (10 to 30 per cent), and least for sulfadiazine (0 to 20 per cent). The acetyl salts of sulfapyridine and sulfathiazole are insoluble in urine, and their precipitation in the urinary tract may lead to hematuria, renal concretions, or anuria. Acetylsulfadiazine is more soluble than sulfadiazine, and urinary complications are less likely to occur from the acetylation of this drug. Forcing fluids and maintaining the urinary output at

more than 1,200 c.c. daily are essential in avoiding urinary complications with the sulfonamide drugs, particularly sulfapyridine, sulfathiazole, and sulfadiazine. Alkalinization of the urine with oral sodium bicarbonate will aid in the ionization of these drugs to the sodium salts, thereby increasing their solubility in urine.

Excretion occurs almost entirely in the urinary tract, although small amounts of sulfathiazole are excreted in the feces. Excretion is rapid with sulfathiazole and slower with sulfadiazine. Impaired renal function will lead to a retention of these drugs. Renal complications are greatest with sulfapyridine, small with sulfadiazine and sulfathiazole, and least with succinylsulfathiazole and sulfanilamide.

Mode of Action.—Briefly, the mode of action of the sulfonamides is unknown. In clinical doses the drugs are bacteriostatic, not bacteriocidal. Experimentally, phagocytes are not necessary for sulfonamide action, but clinically phagocytosis of the bacteria is an important feature in the tissue immunity which is ultimately responsible for the eradication of the offending organisms. The sulfonamides have no direct effect on bacterial toxins. Bacteriostasis apparently results from an interference in bacterial cell metabolism or inactivation of an enzyme-substrate essential for bacterial growth. The main theories of sulfonamide action may be summarized as follows.

1. *Lockwood's Peptone Theory*[12-15]: Peptones or split protein nitrogen interfere with sulfonamide action. Sulfonamide combines with free amino nitrogen of protein degradative product, thereby rendering them unsuitable for bacterial utilization. The clinical implication is clear. The drugs are ineffective in the presence of pus; peptone is a definite sulfonamide inhibitor, and abscesses must be drained surgically. Necrotic tissue also is a sulfonamide-inhibitor substance.

2. *Mellon's Peroxide-Catalase Theory*[16]: Catalase is an enzyme normally destroying the hydrogen peroxide liberated by bacteria. Sulfonamides act as an anticatalase, permitting accumulation of peroxide about cells and bacteria. The high concentration of peroxide produces bacteriostasis. Apparently, the tissues convert sulfonamide into anticatalase. The sulfonamides, however, are effective against some non-peroxide-forming bacteria.

3. *Para-Amino-Benzoic Acid Theory:* Stamp[17] and Woods[18] found a para-amino compound of low molecular weight was necessary for the growth of many bacteria. Because of a close identity to sulfonamide they postulated it to be para-amino-benzoic acid. In vitro and in vivo para-amino-benzoic acid is a strong sulfonamide inhibitor, but it has not been isolated from growing bacteria. The "competitive enzyme" theory has been evolved. Sulfonamide and para-amino-benzoic acid compete for a place in the enzyme substrate system essential for bacterial multiplication. If sulfonamide wins, the enzyme system is inactivated and bacteriostasis results. If para-amino-benzoic acid predominates in the tissues the enzyme system is activated and bacterial multiplication is

rapid. This theory has been further correlated with Lockwood's observations, for areas of tissue destruction and abscess formation are high in para-amino-benzoic acid. Practically, the procaine anesthetics are derived from the para-amino-benzoic acid series and inhibit sulfonamides. Para-amino-benzoic acid may be added to culture media to promote bacterial growth in the presence of sulfonamides.

4. *Oxidation Theory* (Fox[19] and Shaffer[20]): In vivo the sulfonamides are converted to active oxidation products, it is postulated, and, in fact, oxidation products of the sulfonamides are found in the urine, chiefly in the form of glucuronides and sulfates. Sulfonamide bacteriostasis rests upon the production of oxidizing conditions which serve to inactivate enzymes necessary for bacterial growth. This correlates with Mellon's theory. However, the sulfonamides are effective in anaerobic media.

To summarize, the action of sulfonamides is bacteriostatic, preventing overwhelming infections and permitting the mobilization of natural tissue defenses to eradicate the bacteria and evoke recovery. It is assumed that bacteriostasis rests upon the production of oxidizing conditions which inactivate an enzyme or enzyme-substrate necessary for bacterial growth. Peptone and para-amino-benzoic acid are strong sulfonamide inhibitors.

Drug Resistance.—It is recognized that certain organisms that are usually affected greatly by sulfonamides are resistant to them. This resistance may be natural or acquired, and exists for all organisms susceptible to sulfonamide therapy. Clinically, drug resistance is produced most commonly by giving suboptimal doses of the drugs for a relatively long period. Once developed, the organism is resistant to all members of the sulfonamide group, and usually this resistance is permanent.

Dosage.—Optimum concentrations should be obtained rapidly by a large initial dose, and this concentration should be maintained for seventy-two hours. If the drug is effective, beneficial results should be obtained by the third or fourth day at the latest. The drug should be discontinued if ineffective.

For practical purposes the initial oral dose is approximately 0.10 Gm. per kilogram of body weight for sulfanilamide, sulfathiazole, and sulfadiazine. The subsequent maintenance dose is approximately 0.10 Gm. per kilogram of body weight given orally in six divided doses at regular four-hour intervals. For the normal adult this amounts to an initial dose of 4 to 6 Gm., followed by 1 Gm. orally every four hours, day and night.

If oral medication is interdicted, sodium sulfathiazole or sodium sulfadiazine may be given intravenously. The initial dose is 5 Gm. given as a 5 per cent solution in sterile distilled water. The subsequent daily dose for sulfadiazine is 5 Gm., one-half of it to be given in the morning and one-half in the evening. For sulfathiazole, 1½ to 2 Gm.

should be given every six hours. By this method of administration approximately uniform blood concentrations will be maintained.

Recent work both experimentally and clinically[11, 21, 22] demonstrates the safety of subcutaneous administration of 0.5 per cent sodium sulfathiazole and 1 per cent sodium sulfadiazine solutions. Sulfanilamide may also be given subcutaneously in 1 per cent solution, but sodium sulfapyridine must never be used subcutaneously.

The dosage of succinylsulfathiazole is discussed separately. Evidence suggests that sulfates, arsenic and gold compounds, x-ray therapy, and large doses of avertin should not be given simultaneously with sulfonamides. Many prefer to administer vitamins, especially vitamin C, in large doses during sulfonamide medication, believing it diminishes toxicity.

Toxicity.—Toxic symptoms from sulfonamide medication are not uncommon, and one should avoid giving a sulfonamide to a patient known to be sensitive to this group of drugs. Serious toxic manifestations are infrequent in the average patient when a good fluid intake and a daily urinary excretion of more than 1000 c.c. are maintained.

Sulfanilamide very frequently produces nausea and vomiting, cyanosis, dizziness, headache, acidosis, fever, and rash. Agranulocytosis, hemolytic anemia, hepatitis, and jaundice may occur, but hematuria and crystalluria do not appear.

Sulfathiazole is of low toxicity, but hematuria, crystalluria, anuria, urinary tract stones, fever, and dermatitis occur and must be anticipated. Sulfadiazine is the least toxic sulfonamide drug now available. In general, its complications are similar but less frequent than with sulfathiazole. Succinylsulfathiazole is believed to be nontoxic.

It is advisable to stop the drug and force fluids if acidosis, agranulocytosis, hematuria, gastrointestinal disturbances, mental disturbances, fever, or rash appear. It is imperative to stop the drug with the occurrence of anuria, hemolytic anemia, hepatitis, leucopenia with granulocytopenia, or jaundice.

Choice of Sulfonamide.—Sulfanilamide is used rarely because of its frequent minor toxicity and limited range of effectiveness. Sulfathiazole is of low toxicity and is highly effective against staphylococci, pneumococci, hemolytic streptococci, gonococci, *Escherichia coli*, and meningococci. It has the disadvantage of being absorbed and excreted irregularly, and, hence, it is more difficult to maintain with sulfathiazole, a constant effective blood concentration. Also, renal complications occur slightly more frequently with it than with sulfadiazine. Sulfadiazine is less toxic, is rapidly and regularly absorbed, poorly excreted, and possesses a range of effectiveness equal to that of sulfathiazole, except, possibly, in the treatment of staphylococcal infections. With this possible exception, sulfadiazine, when administered systemically, is the drug of choice for all of the previously mentioned infections.

Local Use.—The mere instillation of one of the "wonder drugs" into a wound may lull the thoughtless surgeon into a careless complacency, and deter him from the observance of other fundamental principles essential to kindly healing in a contaminated wound. It must be emphasized at the outset that the local use of sulfonamide in wounds is only one of the present-day adjuncts in the prevention and treatment of infection in contaminated wounds. The vast and recent experiences of the numerous surgeons who have clarified the concepts underlying the management of contaminated wounds have been admirably discussed and summarized by Whipple in a recent monograph.[23] Briefly, Whipple states that the local factors governing wound healing are: (1) amount of necrotic or devitalized tissue present, (2) local blood supply, (3) amount and character of exudate in the wound spaces, (4) number and virulence of infecting organisms, and (5) number and character of foreign bodies. Systemic conditions as (1) age of tissues, (2) hydration of tissues, (3) normal tissue protein, (4) proper vitamin balance, especially of vitamin C, and (5) general circulation and blood picture also influence wound healing. Surgical methods aid wound healing by preventing infection, utilizing the techniques of débridement, instillation of sulfonamides locally both before and after débridement, providing adequate drainage for infected wounds (Orr-Trueta method), avoiding suturing of wounds under tension or the formation of "dead spaces," and insuring adequate immobilization and rest of damaged parts. Chemotherapy, débridement, closed plaster method of Orr and Trueta, blood transfusions, vitamins, plasma, and proper fluid balance are all essential to kindly healing of wounds.

The sulfonamide drugs are valuable aids when properly employed in the management of contaminanted or infected wounds. In civilian practice an increasing number of contaminated or compound wounds may be closed successfully per primam after the local use of sulfonamides, but war wounds must still be permitted to close by secondary intention in the majority of instances, with the possible exceptions of open wounds of the abdomen, chest, hand, or brain. Aside from the fact that more serum may appear in wounds and that healing may be slightly retarded, it has been repeatedly demonstrated that sulfonamides are harmless in the healing of tissues whether implanted in compound fractures, burns, or peritoneal, pleural, or cranial cavities. According to recent reports, sulfathiazole may produce convulsions when applied to the brain.[24]

The factors influencing sulfonamide action are (1) concentration of the drug, (2) concentration and virulence of the offending organisms, (3) amount of sulfonamide-inhibitor substance, and (4) the local blood supply. The solubilities of the various sulfonamides in tissue fluid or plasma at 37° C. are approximately as follows[25]: sulfanilamide, 1,970 mg. per liter; sulfathiazole, 330 mg.; and sulfadiazine, 161 mg. per liter. The rationale for the local use of sulfonamides rests upon the

ability to produce a local tissue concentration 50 to 100 times as high as can be obtained by systemic administration, and to have it persist for a period of twenty-four to forty-eight hours or longer while the implanted drug is being absorbed. The effectiveness of local sulfonamide implantation has been observed in the treatment of compound fractures, contaminated wounds, burns, peritonitis, and other affections. However, the results are not always brilliant and frequently it seems the bacterial infection is merely delayed or attenuated. It must be remembered that the sulfonamides are bacteriostatic in therapeutic doses, not bacteriocidal, and tissue immunity is essential for eradication of all organisms.

The absorption of sulfonamide after local implantation is good, regardless of site, and it is usually complete in eight to twenty-four hours. High blood concentrations can be obtained at that time. Sulfanilamide has a higher local solubility and greater diffusibility in the tissues than sulfathiazole, and creates less exudation of tissue fluids in the wound. At its upper limits of solubility it seems to be as effective an antibacterial agent as are the other sulfonamide compounds at their peaks of local solubility for the majority of organisms ordinarily present in contaminated wounds. Sulfathiazole is less soluble, tends to cake in the tissues, creates more foreign body reaction, and is absorbed over a twenty-four- to forty-eight-hour period or longer. But, since sulfathiazole is effective against a wider variety of organisms and remains longer locally, many surgeons consider it advisable to implant a mixture of equal parts of sulfanilamide-sulfathiazole for local use, using, if available, the microcrystals of sulfathiazole which are more soluble. Sulfadiazine has been shown to be effective on local application, but it has a low solubility. Because of the rapid local absorption of these drugs, it is important to administer a sulfonamide in full doses by mouth or parenterally, and for this sulfadiazine is the drug of choice, regardless of the offending organism. The administration of sulfadiazine should be continued in full doses for seven to ten days.

In an effort at prophylaxis of wound infection, particularly if definitive surgical treatment of the contaminated wound must be delayed for several hours or longer, immediate local implantation of sulfanilamide or a mixture of equal parts of sulfanilamide-sulfathiazole should be carried out. A prophylactic oral or parenteral dose of sulfadiazine is well administered simultaneously. The usual initial dose of sulfadiazine is 4 Gm., and the subsequent maintenance dose is 1 Gm. every six hours, day and night.

The dosage of sulfonamide for local use is approximately 0.10 Gm. per square inch. Up to 20 Gm. may be instilled into larger wounds. More sulfonamide may be instilled if the wound is left open. Practically, the wound need only be "frosted" or "sprinkled" with a thin uniform film of sulfonamide. It is important that the sulfonamide be distributed evenly and uniformly in the wound, and not thoughtlessly poured into

the tissues. Accurate wound hemostasis prevents lavaging of the sulfonamide from its seat of action, and permits adequate contact of the compounds with the contaminated tissues. It is necessary to repeat the local application of sulfonamide to the wound at each dressing until healing is complete.

In orthopedic surgery the incidence of infection in compound fractures in civilians is reduced remarkably by the use of sulfonamides locally, and primary closure is permissible in many cases in which débridement is carried out within the golden period of six to eight hours following injury. Sulfonamide is used also in acute osteomyelitis to tide the patient over the initial period of toxicity while localized abscesses are forming, but abscesses must be surgically drained.[26] In chronic osteomyelitis occasionally primary skin closure may be permitted following radical excision of all involved bone and local "frosting" with sulfonamide.

It has long been recognized that the necrotic or purulent material in wounds will nullify greatly the beneficial effects of sulfonamides in the wounds. Necrotic, contaminated, or purulent material is a strong sulfonamide-inhibitor, and these substances should be reduced to a minimum in the wound by gentle irrigation of the wound or by wet dressings. Recently, evidence has been offered to suggest a potentiation of sulfonamide activity by the concurrent use of mild oxidizing agents, particularly of 1:3,300 solution of azochloramide.[27] Allantoin or urea has also been suggested as effective in combating the effects of the sulfonamide-inhibitor substances in pus or necrotic material.[28] The entire field of sulfonamide potentiation has only recently been subjected to scientific investigation and future developments may soon alter the principles underlying the local application of sulfonamides.

Gas gangrene is best treated by initial débridement of the wound, application of a mixture of sulfanilamide-sulfathiazole locally, full doses of sulfadiazine by mouth, and the administration of antitoxin. If these measures fail, amputation may be necessary as a lifesaving procedure. X-ray therapy is of dubious value and should not be used with the sulfonamides.

For burns, innumerable dressings containing a sulfonamide have been suggested. A good sulfonamide dressing is 3 per cent sulfadiazine in 8 per cent triethanolamine,[29] applied hourly until a thin, pliable, elastic, and translucent eschar results. Sulfonamide in solid form or as wet dressings has been used to prepare areas for early skin grafting. Another excellent technique for preparing an infected area for skin grafting is to frost it daily with a sulfanilamide-sulfathiazole mixture and then cover it with wet dressings of 1:3,300 azochloramide. Potentiation of the sulfonamide activity may thereby occur.[27]

Sulfonamide applied locally into the peritoneal and other body cavities is beneficial in prevention of infection after contamination of these cavities has resulted from disease or accident. Either sulfanila-

mide or a mixture of sulfanilamide-sulfathiazole may be used. Absorption is particularly rapid from the peritoneal cavity and systemic administration of the drug, preferably sulfadiazine, is imperative.

Sodium sulfapyridine is so alkaline (pH 10.6) that it must never be used for local implantation. Tissue necrosis with subsequent sloughing has commonly ensued. Recent experimental and clinical studies on the local use of the sodium salts of sulfathiazole and sulfadiazine[11] seem to indicate that these salts, especially the sodium sulfadiazine, may be safely implanted in the subcutaneous or intramuscular tissues. The pH of a concentrated solution of sodium sulfadiazine (over 5 per cent) is 9.4, of sodium sulfathiazole 9.8. The local application of the sodium salts of sulfathiazole and especially of sulfadiazine is an advance which would obviate the insolubility and caking of these drugs in the wound and would permit the far greater antibacterial potency of these two drugs over sulfanilamide. At present, however, insufficient evidence exists to warrant the intraperitoneal use of any of the sodium salts, and they should be used with caution in the wounds of soft tissues.

Perrin Long, in a recent article,[30] summarizes well the present status of local sulfonamide therapy. In his opinion a combination of systemic with local therapy offers the best chance for prevention of wound infection and for its cure once an infection has become established. He recommends sulfadiazine by mouth in doses high enough to maintain a blood concentration of 4 to 7 mg. per 100 c.c. as the most desirable drug for systemic administration; sulfanilamide alone is recommended for local use. "From all points of view, sulfanilamide seems at the present time to be the drug of choice for topical application. It is to be remembered that necrotic tissue and pus contain sulfonamide inhibitors and that every effort should be made to eliminate these inhibitors before sulfanilamide is applied locally. Care should always be taken to prevent the caking of sulfanilamide in the wound, and this can be accomplished by applying moist gauze dressings following the application of sulfanilamide to the wound. In the absence of clinical infection, there is little reason to continue oral therapy with sulfadiazine more than five to seven days. However, to prevent secondary infections from occurring after primary prophylaxis has been successful, it is necessary to apply sulfanilamide powder locally until wound healing is complete." No one disputes the effectiveness of sulfanilamide for local use in contaminated wounds, but many surgeons prefer a mixture of sulfanilamide-sulfathiazole in equal parts, for reasons already explained.

Urinary Tract.—The common offending organisms in infections of the urinary tract are *Esch. coli, Aerobacter aerogenes,* staphylococci, *Proteus vulgaris,* and *Str. fecalis.* Infections with the streptococci of Lancefield Group A, which are responsible for serious streptococcal infections in man, are extremely rare in the urinary tract. The organisms of the coli group and staphylococcal group are very susceptible

to sulfathiazole or sulfadiazine, sulfathiazole possibly being preferable for coagulase positive staphylococci. *P. vulgaris* and *Str. fecalis* respond poorly to sulfanilamide, and only moderately to full doses of sulfathiazole or sulfadiazine. Sulfathiazole or sulfadiazine in doses of 3 to 6 Gm. daily yields in the urine a concentration of 20 to 75 mg. per 100 c.c. This dosage is sufficient to inhibit the growth of most organisms commonly present in urinary tract infections whether one is dealing with a cystitis or pyelonephritis. Any obstruction to the free flow of urine must be removed, for stasis predisposes to and aggravates any infection of the urinary tract. Urinary diuresis in itself is of value in the treatment of urinary tract infections, and decreases the incidence of renal complications from sulfonamide therapy. Fluids should be forced to at least 3000 c.c. daily, and a daily output of more than 1000 c.c. must be maintained. Alkalinization of the urine by oral bicarbonate or sodium citrate is advisable. Also, sulfonamides in smaller doses are used prophylactically prior to instrumentation of the urinary tract and postoperatively for an inlying catheter.

The sulfonamide effect is one of bacteriostasis, and tissue immunity evokes final recovery. Chronic infections without demonstrable obstruction are difficult to cure by any drug.

Intestinal Antisepsis.—Sulfaguanidine was developed in an attempt to reduce the number of bacteria in the colon preceding operations upon the gastrointestinal tract. This drug reduced the coliform count in the stool to a great extent, but it proved to be absorbed irregularly, occasionally was toxic, and was inactive in the presence of ulcerative lesions of the intestines. Succinylsulfathiazole (sulfasuxidine) was introduced later by Poth and Knotts,[31] Firor,[32] and Poth,[33] and from the clinical and experimental studies reported this drug appears to be exceedingly promising as an intestinal antiseptic. It is strongly bacteriostatic, absorbed poorly, nontoxic, and is effective in the presence of ulcerative lesions of the bowel. At most 5 per cent of the drug is excreted in the urine, and because of its rapid excretion and relatively high solubility (450 mg. per cent) renal complications have not been encountered.

The initial dose is 0.25 Gm. per kilogram of body weight, and the subsequent daily dose is 0.25 Gm. per kilogram given in six divided doses. Larger doses are tolerated if given at hourly intervals, and up to 0.5 Gm. per kilogram per day may be given with safety. In one to seven days the stools become semifluid, odorless, more mucoid, and reduced in bulk. The count of colon bacilli falls from 10,000,000 per gram of wet stool to approximately 1000 per gram of wet stool. The mechanism of action is similar to that of other sulfonamides, and the active substance is probably sulfathiazole, formed by hydrolysis by bacterial cells in the large bowel. The concentration of sulfathiazole in the feces with clinical doses is 50 to 200 mg. per cent. To be effective

the drug must come into prolonged intimate contact with all portions of the bowel mucosa.

The action of the drug is impaired appreciably by diarrhea, constipation with inspissated stools, and the simultaneous use of liquid petrolatum or other catharties. Larger doses are required in the presence of ulcerative lesions, but the drug remains effective. The proper preoperative preparation consists in the omission of enemas, catharties, and petrolatum. A nonresidual diet is advisable. Full doses of the drug should be administered, and the optimum time for surgery may be judged by bacterial counts on the stool or by observations of the character of the stool. Since the drug is well tolerated, with little nausea and vomiting, it may be given postoperatively as soon as the patient takes water. Breaking the tablets up and dissolving them in water facilitates administration. In practice, the drug has failed only in the presence of severe diarrhea or of a blind loop obstruction.

It must be emphasized that succinylsulfathiazole is merely an adjunct to surgery of the gastrointestinal tract, and should never permit one to nullify the observance of well-established surgical principles in the pre- and postoperative care. Experience with this drug is still limited. However, it is not effective in combating typhoid, paratyphoid, *Str. fecalis*, or the proteus group of organisms.

SUMMARY

The sulfonamide drugs are powerful chemotherapeutic agents, specific in their action on certain organisms and without effect on others. Those organisms not affected may be resistant naturally, or they may have an acquired resistance. Their mode of action is not known accurately, but it is probable that bacteriostasis rests upon the inactivation of an enzyme or enzyme-substrate system necessary for bacterial growth. The main theories of the mode of action have been presented. Peptone, para-amino-benzoic acid, necrotic tissue, and certain bacterial and yeast extracts inhibit the bacteriostatic action of these drugs. The sulfonamides are essentially bacteriostatic not bacteriocidal, and the natural defense mechanisms of the body have to complete the destruction of the bacteria. Sulfonamides inhibit bacterial growth, and prevent overwhelming intoxication by bacterial infection but tissue immunity must be mobilized to realize complete recovery.

Sulfathiazole is regarded as the drug of choice for staphylococcal infections, but, clinically, it is probably no more effective than sulfadiazine, which is slightly less toxic. For all other infections which are susceptible to the sulfonamides, sulfadiazine is the drug of choice. For local use sulfanilamide or a mixture of sulfanilamide and sulfathiazole is the best, regardless of the site of local implantation. The local use of sodium sulfadiazine and sodium sulfathiazole for soft tissue wounds seems warranted in consideration of recent studies, but their

intraperitoneal use is still counseled against. Succinylsulfathiazole (sulfasuxidine) at the moment is the best drug for intestinal antisepsis. The sulfonamides are merely desirable surgical adjuncts and one must never fail to recognize the importance of well-established surgical principles. The sulfonamides are dangerous therapeutic weapons; their toxicity must be anticipated and toxic symptoms treated vigorously if they occur.

The author wishes to express his gratitude to F. L. Reichert, W. C. Cutting, and J. F. Menke for their assistance in the preparation of this paper.

REFERENCES

1. Domagk, G.: Deutsche med. Wchnschr. **61**: 250, 1935.
2. Whitby, L. E. H.: Lancet **1**: 1210, 1938.
3. Marshall, E. K., Jr., and Long, P. H.: J. A. M. A. **112**: 1671, 1939.
4. Fosbinder, R. J., and Walter, L. A.: J. Am. Chem. Soc. **61**: 2032, 1939.
5. Lott, W. A., and Bergeim, F. H.: J. Am. Chem. Soc. **61**: 3593, 1939.
6. Roblin, R. O., Jr., Williams, J. H., Winnick, P. S., and English, J. P.: J. Am. Chem. Soc. **62**: 2002, 1940.
7. Finland, M., Peterson, O. L., and Goodwin, R. A.: Ann. Int. Med. **17**: 6, 920, 1942.
8. Marshall, E. K., Jr., Braxton, A. C., White, H. J., and Litchfield, J. T.: Bull. Johns Hopkins Hosp. **67**: 163, 1940.
9. Poth, E. J., and Firor, W. M.: Ann. Surg. **114**: 663, 1941.
10. Jensen, N. K., Johnsrud, L. W., and Nelson, M. C.: SURGERY **6**: 1, 1939.
11. Fox, C. L., Jr.: Arch. Surg. **45**: 754, 1942.
12. Lockwood, J. S., and Lynch, H. M.: J. Immunol. **35**: 155, 1938.
13. Lockwood, J. S.: J. A. M. A. **115**: 1190, 1940.
14. Lockwood, J. S.: Surg. Gynec. & Obst. **72**: 307 (2A), 1941.
15. Lockwood, J. S., and Lynch, H. M.: J. A. M. A. **114**: 935, 1940.
16. Locke, A., Main, E. R., and Mellon, R. P.: Science **88**: 620, 1938.
17. Stamp, T. C.: Lancet **2**: 10, 1935.
18. Woods, D. D.: Brit. J. Exper. Path. **21**: 74, 1940.
19. Fox, C. L., Jr.: Am. J. M. Sc. **199**: 487, 1940.
20. Shaffer, A.: Science **89**: 547, 1939.
21. Lyons, J. J. A., Climenko, D. R., and Gorham, L. W.: J. Clin. Investigation **41**: 648, 1942.
22. Taplin, G. V., Custer, E. A., and Young, L. E.: J. A. M. A. **121**: 5, 313, 1943.
23. Whipple, A. O.: Military Surgery Manual No. 5, Burns, Shock, Wound Healing, and Vascular Injuries, Philadelphia, 1943, W. B. Saunders Company, p. 177-194.
24. Pilcher, C., Angelucci, R., and Meacham, W. F.: J. A. M. A. **119**: 927, 1942.
25. Clark, W. G., Strakosch, E. A., and Levitan, N. I.: J. Lab. & Clin. Med. **28**: 188, 1942.
26. Wilson, I. C., and McKeever, F. M.: J. Bone & Joint Surg. **25**: 41-48, 1943.
27. Schmelkes, F. C., and Wyss, O.: Proc. Soc. Exper. Biol. & Med. **49**: 263, 1942.
28. Veal, J. R., and Klepser, R. G.: SURGERY **10**: 947, 1941.
29. Pickrell, K. L.: Bull. Johns Hopkins Hosp. **69**: 217, 1941.
30. Long, P. H.: J. A. M. A. **121**: 303, 1943.
31. Poth, E. J., and Knotts, F. L.: Arch. Surg. **44**: 208, 1942.
32. Firor, W. M.: Ann. Surg. **115**: 829, 1942.
33. Poth, E. J.: J. A. M. A. **120**: 265, 1942.

Book Reviews

Physiology in Aviation. By Chalmers L. Gemmill, B.S., M.D., Commander, M. C., U. S. N. R., Associate Professor in Physiology, Johns Hopkins University, School of Medicine, Baltimore, Md., Instructor in Physiology, School of Medicine, Naval Air Station, Pensacola, Fla. Pp. 124, with 18 tables. Springfield, Ill., 1943, Charles C Thomas, Publisher. $2.

This book by Gemmill is a primer on the subject covered by its title; although brief, it is not vague and reflects its author's valuable teaching experience. The preface states it to be material covered in the lectures on physiology in the School of Aviation Medicine, Naval Air Station, Pensacola, Fla. It would seem to be an excellent guide for medical personnel who give instruction to aviators on the physiologic disturbances encountered in flight.

The Management of Fractures, Dislocations, and Sprains. By John Albert Key, M.D., and H. Earle Conwell, M.D., F. A. C. S. Ed. 3. St. Louis, 1942. The C. V. Mosby Company. $12.50.

The new third edition of this book contains 1,300 pages with many illustrations, photographs, and roentgenograms. Since the publication of the first edition in 1934, this book represents the best in its field published by American authors, and is not overshadowed by any book in any language.

Along with revision of the chapter on compound fractures, a section also has been added on war wounds. This new feature will be both attractive and beneficial to men who will be called upon to treat patients in the armed forces.

The chapters on fractures of the spine, hip, humerus, and foot have been revised to some extent.

With the advent of war, many trained men have been and are being called into the services. This leaves more untrained men at home to care for the civilian population. It seems that a more thorough description of the technique of manipulation and operative treatment of fractures might be of great benefit to these men.

Not only have the authors considered the management of acute injuries, but they have, in many instances, discussed and outlined the treatment of old injuries requiring reconstructive surgery. Many photographs and x-rays have been included to elucidate better the diagnosis, treatment, and end result in a variety of cases.

This book should be in the hands of all men who are doing fracture work today.

Announcing

SURFACE ACTIVE SALINE MIXTURE OF

Azochloramid

REG. U.S. PAT. OFF.

In this new preparation the acknowledged bactericidal power of aqueous solutions of Azochloramid* gains new clinical effectiveness by the addition of sodium tetradecyl sulfate—a surface active compound.

The solution of Surface Active Saline Mixture of Azochloramid contains: Azochloramid (1:3300)—noted for its non-selective, persistent bactericidal action—*and* sodium tetradecyl sulfate (1:1000)—demonstrated to be an effective dispersing agent and surface tension depressor. It is isotonic and buffered to pH 7.4.

**Brand of* CHLOROAZODIN U. S. P.

Clinical reports attest the value of this new *bactericide—wetting agent* solution. It is effective for either prophylaxis or treatment of localized infection and is especially indicated where dispersion and removal of pus and débris from infected wound surfaces and cavities are essential. Physicians will find wide use for this stable chlorine solution as a lavage during surgical débridement, for irrigations and instillations, for wet dressings and for hot compresses.

☆ ☆ ☆

Available in powder form in bottles to prepare 1 gallon and 25 gallons of the aqueous solution at hospital and prescription pharmacies. Literature and samples on request.

ARMY E NAVY

BUY BONDS

WALLACE & TIERNAN PRODUCTS, INC.

BELLEVILLE, NEW JERSEY, U.S.A.

W & J

Authoritative — Up-to-the-Minute — Complete

CURRENT OBSTETRICS AND GYNECOLOGY

Proceedings of the Second

AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY

A correlated program of essays, panel discussions and symposia epitomizing everything important and new in the fields of obstetrics and gynecology. The subject material, carefully integrated in advance, is presented under the strict criteria of question and answer discussions. Authors are unimpeachable authorities—each in his respective field. Discussors are especially selected for experience, critical ability. Analyses and summaries are—as a result—the last word. No stone is left unturned. The result is:

A Work Absolutely Essential to Specialist, General Practitioner, Nurse, Hospital Executive and Maternal and Child-Welfare Worker

Among the Contributors Are:

Fred L. Adair	Nicholson J. Eastman	Edward Allen
Aura E. Severinghaus	Herbert E. Schmitz	Robert D. Mussey
Robert Latou Dickinson	E. D. Plass	J. P. Greenhill
G. D. Royston	I. C. Rubin	E. G. Waters
Carl G. Hartman	Abner I. Weisman	Harry W. Mayes
R. S. Siddall	David S. Hillis	Alan F. Guttmacher
John L. Parks	Lewis C. Scheffey	Philip Levine
Alex E. Brown	A. W. Diddle	A. N. Arneson
E. Granville Crabtree	James R. Reinberger	Sidney O. Levinson
Curtis J. Lund	Lyman W. Mason	Paul F. Fletcher

and over sixty others

I *Almost every important teaching institution represented.*

II *Obstetrics, Gynecology, Obstetrical Hospital Management, Obstetrical Nursing, Public Health and Social Service Aspects.*

III *A complete correlated refresher course absolutely up to date.*

Price, $5.50

PUBLISHED BY THE WESTERN JOURNAL OF SURGERY PUBLISHING COMPANY, PORTLAND, OREGON, FOR THE AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY

To: 8-43

THE AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY
650 Rush Street
Chicago, Illinois

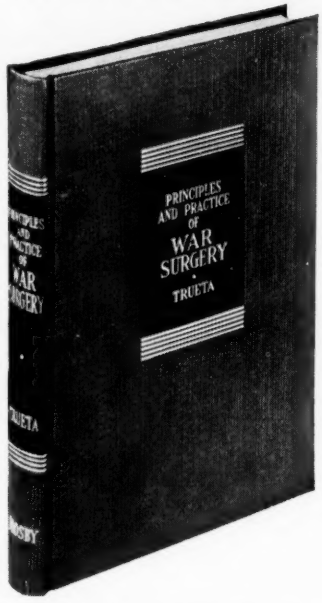
Please place my order for one copy of the 1942 Transactions, at $5.50 per volume, for which check is enclosed (or) you may bill me when volume is shipped.

Name _____ M.D.

Address _____ City _____ State _____

PRINCIPLES AND PRACTICE OF

WAR SURGERY



by J. TRUETA, M.D.

Formerly Director of Surgery, General Hospital of Catalonia, University of Barcelona; Assistant Surgeon (E.M.S.) Wingfield-Morris Orthopaedic Hospital; Acting Surgeon-in-Charge, Accident Service, Radcliffe Infirmary, Oxford. 425 pages, 144 illustrations. PRICE, $6.50.

5-Point TRUETA *Technic*

1. **Prompt surgical treatment.**
2. **Cleansing of the wound.**
3. **Excision of the wound.**
4. **Provision of drainage.**
5. **Immobilization in a plaster-of-Paris cast.**

Listed above are the five essential principles in the biological treatment of wounds as formulated by Trueta, each and every one of which must be applied to ensure the greatest possible success.

In this new book "PRINCIPLES AND PRACTICE OF WAR SURGERY," Trueta sets forth in complete detail these procedures which he has adopted as a result of his experience in the Spanish War and in World War II. However the book is not confined to these methods alone, but deals fully with such important subjects as shock, transfusion, aerobic and anaerobic infections, including gas gangrene and tetanus, chemotherapy, antiseptics, anesthesia, skin grafting, amputation, and treatment of burns.

Graphic illustrations such as those reproduced here supplement the text matter, supplying step-by-step visual guidance. You won't want to miss having this authoritative text. Send for it today!

The C. V. Mosby Company MJ
3525 Pine Blvd., St. Louis 3, Mo.

Gentlemen: Send me a copy of Trueta—Principles and Practice of War Surgery. Price, $6.50.

____Attached is my check. ____Charge my account.

Dr. _____

Address _____

Just Published!

Titus'

ATLAS OF OBSTETRIC TECHNIC

by **PAUL TITUS, M.D.**

Obstetrician and Gynecologist to the St. Margaret Memorial Hospital, Pittsburgh; Secretary, American Board of Obstetrics and Gynecology.

•

Illustrations by **E. M. SHACKELFORD,** Medical Illustrator, John C. Oliver Memorial Research Foundation.

178 pages, 193 illustrations.

PRICE, $7.00

•

CONTENTS

Introduction. General. Pelvimetry. Minor Operations During Pregnancy. Major Operations During Pregnancy. Abortions. Ectopic Pregnancy. Induction of Labor and Enlargement of Cervical Orifice. Spontaneous Deliveries—Forceps Deliveries. Management of Birth Canal Injuries. Cesarean Section. Mutilating Operations. Third or Placental Operation. Postpartum Procedures. Sterility.

With complete clarity and accuracy, this new book pictures for you modern obstetric technic now accepted as standard for normal and operative deliveries, as well as various complications of pregnancy and the puerperium.

"ATLAS OF OBSTETRIC TECHNIC" is essentially a book on clinical practice. It may be used as a supplement to the usual textbook of obstetrics, which for lack of space must omit illustrations of many important phases of technic. However, it has its own definite and separate function—namely, the teaching of both normal and operative obstetrics by visual means through the medium of carefully prepared illustrations. With its guidance you can easily modernize your general obstetric technic, quickly refresh your knowledge when faced with a complicated case requiring operative interference.

These illustrations have been prepared from life-sketches made in the delivery and operating rooms of the St. Margaret Memorial Hospital. Dr. Titus has limited the text to brief descriptions of the details of technics shown in the drawings.

Mail Coupon TODAY!

THE C. V. MOSBY COMPANY MJ
3525 Pine Blvd.
St. Louis (3), Mo.

Gentlemen: Send me Titus' "ATLAS OF OBSTETRIC TECHNIC" immediately. The price is $7.00. --Attached is my check. --Charge my account.

Dr._____

Address_____

GOOD STRATEGY SUGGESTS

EXCELSIOR SPRINGS
MISSOURI

●RIDING ●HIKING
●GOLF ●ALL OUTDOOR ACTIVITIES
●HEALTH GIVING MINERAL WATERS

SEND FOR LOW AMERICAN PLAN RATES

THE ELMS HOTEL

FOR THE EXACTING GUEST

It's Baltimore's Best

—best for accommodations that provide a monopoly on luxury.
—best for location that places you in the principal downtown district, near business contacts and pleasure places.
—best for streamline service that offers you all the modern guest facilities.
—best because of these moderately priced public rooms—

MAIN DINING ROOM, NEW CHESAPEAKE LOUNGE, COFFEE SHOP

450 Large Guest Rooms

All rooms with bath, radio, and circulating ice water.

Single Rooms With Bath, $3.00 up
Double Rooms With Bath, $4.50 up

The Emerson HOTEL
BALTIMORE, MD. O.G. CLEMENTS, MGR.

Lighting and Leading the Way to the 5th FREEDOM* . . . .

*The right to enjoy health

Your part in America's Victory Program requires energy, vigor and health. Keep fit by relaxing at this world-famous health spa in the beautiful Ouachita Mountains. Horseback riding, golf, tennis, hiking, boating and fishing on Lakes Hamilton & Catherine; and countless other recreations.

HOT SPRINGS
NATIONAL PARK • ARKANSAS

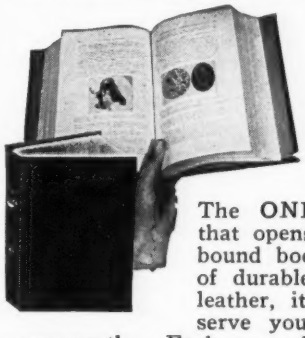
At the Majestic, beautifully furnished 2, 3 & 4 room apartments and single rooms, with or without bath. Government supervised bath house in hotel.

DAILY RATES FROM $2.

Majestic
HOTEL, APARTMENTS AND BATHS
For complete information – WALTER E. DAVIS, Manager,

Direction: SOUTHWEST HOTELS INC.

A Handsome Permanent Binder for SURGERY



ONLY $1.25

The ONLY binder that opens flat as a bound book! Made of durable imitation leather, it will preserve your journals permanently. Each cover holds 6 issues, one volume (2 volumes published each year). Do your own binding at home in a few minutes. Instructions easy to follow.

Mail coupon for full information and binder on 10-day free trial.

MAIL COUPON TODAY

SUCKERT LOOSE LEAF COVER CO.
234 W. Larned St., Detroit, Michigan

Mail postpaid _____ binders for "SURGERY" for year _____. Will remit in 10 days or return bindings collect.

Name _____

Address _____

INDEX TO ADVERTISERS

Please mention "SURGERY" when writing to our advertisers—It identifies you

Articles to Appear in Early Issues ----------3rd Cover

Ciba Pharmaceutical Products, Inc. (Digifolin) ---------- 11
Crescent Surgical Sales Co., Inc. (Surgical Blades and Handles)-- 10

Davis & Geck, Inc. (Surgilon)------ 1

Elms Hotel (Excelsior Springs, Mo.) 19
Emerson Hotel, The (Baltimore, Md.) 19

Hoffmann-La Roche, Inc. (Prostigmin) ----------4th Cover

Johnson & Johnson (Sutures)-------
--------Insert between pp. 12 and 13

Lilly and Company, Eli---------- 14
Lippincott Co., J. B. (Surgical Books) 6

Majestic Hotel (Hot Springs, Ark.) 19
Merrell Company, The William S. (Ceepryn) ----------4, 5

O'Leary, Inc., Lydia (Covermark)-- 2

Parker, White & Heyl, Inc. (Formaldehyde Germicide) ---------- 9

Singer Sewing Machine Company (Surgical Stitching Instrument)-- 7
Sklar Manufacturing Company, J. (Surgical Instruments) ---------- 13
Stearns & Company, Frederick (Parenamine) ---------- 3
Suckert Loose Leaf Cover Co. (Journal Binder) ---------- 19

Wallace & Tiernan Products, Inc. (Azochloramid) ---------- 15
Warner & Co., Inc., William R. ----- 12
Western Journal of Surgery Publishing Company ---------- 16

All possible care is exercised in the preparation of this index. The publishers are not responsible for any errors or omissions.

Will You Sell Your Back Copies . . . To Re-establish a Destroyed Library?

The Committee on Aid to Libraries in War Areas, of the American Library Association, is making every possible effort to secure war-published issues of medical journals for the restoration of the devastated old and honored institutional scientific libraries of all nations. We have contracted with this Committee to supply copies of SURGERY. We are out of stock of copies of the following issues, and will pay fifty-five cents a copy—the amount we are charging the Committee—for them. *Address yours to: A. W. Volland, Circulation Manager, The C. V. Mosby Company, 3525 Pine Blvd., St. Louis 3, Mo.*

Vol. 8, No. 2 Aug., 1940
Vol. 8, No. 3 Sept., 1940

Articles to appear in early issues of

SURGERY

PERFORATION OF THE CERVICAL ESOPHAGUS WITH MEDIASTINITIS.
By Kenneth D. Grace, M.D., La Grange, Ga., and Thomas M. Irwin, M.D., Orlando, Fla.

THE INFLUENCE OF DUODENAL CONTENTS ON INTRAGASTRIC ACIDITY.
By Authi Kesavalu, M.D., and Frank C. Mann, M.D., Rochester, Minn.

ABDOMINAL PUNCTURE AS A DIAGNOSTIC AID.
By Charles M. Henry, M.D., and C. Fremont Vale, M.D., Detroit, Mich.

A SIMPLIFIED SUTURE-TESTING APPARATUS.
By Clarence Dennis, M.D., Minneapolis, Minn.

SULFATHIAZOLE IN CHRONIC OSTEOMYELITIS.
By James W. Toumey, M.D., Boston, Mass.

A NEW PRACTICAL SIGMOIDOSCOPE.
By Cecil P. G. Wakeley, C.B., D.Sc., F.R.C.S., F.A.C.S., Hants, Eng.

DESCENT OF THE TESTIS: ANATOMICAL AND HORMONAL CONSIDERATIONS.
By L. J. Wells, M.D., Minneapolis, Minn.

A CONSIDERATION OF THE PRESENT STATUS OF THE SHOCK PROBLEM (PROBLEMS ON SHOCKS).
By Alfred Blalock, M.D., Baltimore, Md.

THE TREATMENT OF ACUTE EMPYEMA BY CONTINUOUS TIDAL IRRIGATION.
By Edgar J. Poth, Ph.D., M.D., Galveston, Texas, and Mary E. Mathes, M.D., San Francisco, Calif.

DESTRUCTIVE ANGIOCYSTIC DISEASE OF THE PANCREAS.
By W. Wayne Babcock, M.D., Machteld E. Sano, M.D., Philadelphia, Pa., and Stuart B. Gibson, M.D., Williamsport, Pa.

SOLITARY ECCENTRIC (CORTICAL) ABSCESS IN BONE.
By R. C. Brown, M.D., Minneapolis, Minn., and Ralph K. Ghormley, M.D., Rochester, Minn.

LIGATION OF THE SUPERIOR MESENTERIC VEIN.
By Edward Schnug, M.D., Cincinnati, Ohio.

A STUDY OF THE HEALING OF ABDOMINAL OPERATIVE WOUNDS FOLLOWING CLOSURE OF PERFORATED ULCERS OF THE STOMACH AND DUODENUM.
By Richard H. Meade, Jr., M.D., Philadelphia, Pa.

Colon Symposium

THE BLOOD SUPPLY OF THE LARGE BOWEL WITH REFERENCE TO RESECTION.
By Albert O. Singleton, M.D., Galveston, Texas.

PRIMARY RESECTION (CLOSED ANASTOMOSIS) OF THE COLON AND RECTOSIGMOID.
By Owen H. Wangensteen, M.D., Minneapolis, Minn.

THE MANAGEMENT OF POLYPS OCCURRING IN THE RECTUM AND COLON.
By Vernon C. David, M.D., Chicago, Ill.

CANCER OF THE COLON.
By M. M. Zinninger, M.D., and Paul I. Hoxworth, M.D., Cincinnati, Ohio.

CONSIDERATION OF ELECTIVE SURGICAL PROCEDURES IN VARIOUS SEGMENTS OF THE COLON.
By Thomas E. Jones, M.D., Cleveland, Ohio.

CARCINOMA OF THE COLON AND RECTUM.
By Richard B. Cattell, M.D., Boston, Mass.

CARCINOMA OF THE COLON.
By Arthur W. Allen, M.D., Boston, Mass.

SURGERY OF THE TERMINAL ILEUM, CECUM, AND RIGHT COLON.
By Allen O. Whipple, M.D., New York, N. Y.

ANTERIOR RESECTION OF THE RECTOSIGMOID AND UPPER RECTUM WITH RE-ESTABLISHMENT OF CONTINUITY.
By Laurence Sidney Fallis, M.D., F.R.C.S., Detroit, Mich.

Foresight in Surgery

Prostigmin Methylsulfate 'Roche' maintains intestinal and bladder tone, minimizing the incidence of abdominal distention and urinary retention following surgery. Surgeons who have the foresight to administer Prostigmin preoperatively usually prevent "gas pains" and avoid the necessity for catheterization during the postoperative period. Prostigmin is used by many leading surgeons as a prophylactic routine measure and is regarded as a valuable aid in affording a smoother convalescence to patients whose recovery otherwise might be retarded by post-operative complications due to intestinal or bladder atony . . .
HOFFMANN-LA ROCHE, INC., ROCHE PARK, NUTLEY, NEW JERSEY

• Supplied in two strengths: 1:4000 solution for prevention or prophylaxis; 1:2000 solution for treatment.

PROSTIGMIN *'Roche'*